The Confidential Enquiry into Perioperative Small Animal Fatalities

By

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Abstract

This thesis represents a large scale practice based prospective epidemiological study, undertaken to estimate the species-specific risks of anaesthetic-related death in small animals in the UK, to identify risk factors for anaesthetic-related death in dogs, cats and rabbits and to make recommendations to improve the practice of small animal veterinary anaesthesia.

A nested case-control study was undertaken in a cohort of small animals anaesthetised at a group of veterinary practices and referral institutions in the UK. A record of all small animals anaesthetised at the centres during their period of participation and whether they were dead or alive, 48 hours later, was made. Anaesthetic-related death (a case) was defined as perioperative death within 48 hours of termination of the procedure, except where death was due solely to inoperable surgical or pre-existing medical conditions. Cases were compared to prospectively randomly selected controls in dogs and cats. Matched controls from the same clinic as the individual cases were selected in rabbits. Sick cases (poor health status) were also compared to randomly selected sick controls in dogs and cats. Following univariable screening, logistic regression modelling was undertaken. Mixed effects models treating clinic as the random effect were developed for dogs and cats and a conditional logistic regression model was built for rabbit mortality.

One hundred and seventeen centres participated in the study between June 2002 and June 2004. During that time, 98,036 dogs, 79,178 cats and 8,209 rabbits were anaesthetised or sedated and 163, 189 and 114 anaesthetic-related deaths were identified respectively, resulting in risks of death of 0.17% (95% Confidence Interval (95% CI) 0.14 – 0.19%) in dogs, 0.24% (0.21 – 0.27%) in cats and 1.39% (1.11 – 1.64%) in rabbits. Other small animal species tended to have higher risks. In rabbits, poor health status, procedures lasting 30 or more minutes, and major procedures were associated with increased odds and the veterinary surgeon being very familiar with the anaesthetic used with reduced odds of anaesthetic-related death. In dogs, increased odds were associated with poor health status, extremes of age and weight, increasing procedure urgency, complexity and duration, and with mask induction of anaesthesia and maintenance with halothane. In the sick dog study, increased odds were associated with poor health status, extremes of weight, increasing procedural urgency, halothane

anaesthesia and controlled ventilation; preoperative blood testing was associated with reduced odds. In cats, poor health status, extremes of weight, increasing age, increasing procedural urgency and complexity, endotracheal intubation and perioperative fluid therapy were associated with increased odds; pulse and pulse oximetry monitoring were associated with reduced odds. In the sick cat study, poor health status, increasing weight and age, and perioperative fluids were associated with increased odds, pulse and pulse oximetry monitoring and the use of nitrous oxide were associated with reduced odds.

The risks of anaesthetic-related mortality have decreased in dogs and cats since the last UK study, though they remain substantially greater than the risk reported in man. The risks in other species appear higher and should be particularly targeted for improvement. Patient health status, age and weight, and procedural urgency, complexity and duration would appear valuable factors to aid assessment of anaesthetic risk and identify patients that require intensive perioperative management. The use of isoflurane anaesthesia and the avoidance of mask inductions in dogs, the judicial use of endotracheal intubation in cats and increasing veterinarian familiarity with the anaesthetic used in rabbits could reduce the risk of anaesthetic-related death. The merits of pulse and pulse oximetry monitoring and fluid therapy require further evaluation.

Memorandum

This thesis represents the unaided work of the author, except where acknowledged. The views expressed in this work are those of the author and not necessarily of the University.

Dave Brodbelt

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Preface

There is very little reporting of small animal perioperative complications in the veterinary literature. Not since the 1980's were anaesthetic complications evaluated in small animal practice in the UK (Clarke and Hall 1990). During the 1990's, international work has estimated the risk of anaesthetic death in small animal practice and identified major risk factors for anaesthetic-related death (Dodman and Lamb 1992; Rintasalo and Vainio 1995; Dyson, Maxie et al. 1998; Joubert 2000), but this work also is now out of date and may be less relevant to current UK practice. New drugs, techniques and equipment have been introduced to UK veterinary practice and the risk associated with small animal anaesthesia needs re-evaluation. The aims of this study were to prospectively estimate risks of anaesthetic-related death in small animals in the UK, to identify risk factors for anaesthetic-related death in dogs, cats and rabbits and to make recommendations to reduce the risk of death in small animal anaesthesia, based on their scientific understanding.

Specific hypotheses pertaining to the risk factors in dogs, cats and rabbits were developed prior to the study based on previous published work and clinical experience. They included that:

a. Sick patients are at increased risks of death compared to healthy patients.

b. Acepromazine, propofol and isoflurane are associated with reduced risk in dogs and cats.

c. The use of medetomidine is associated with increased risk.

d. The use of intraoperative fluid and having a separate person monitoring anaesthesia are associated with a reduction in the risk.

e. Endotracheal intubation in cats is associated with increased risk.

f. Mask inductions are associated with increased risk in rabbits.

A study was designed to test these hypotheses and a pilot study was then undertaken, to test data collection tools and to check the design was appropriate. In the light of the pilot study, the hypothesis that medetomidine was associated with increased odds of anaesthetic-related death was revised to a reduction in odds in dogs and cats.

The thesis is divided into eight chapters, comprising the literature review, a general materials and methods chapter, results and an overall discussion chapter. The characteristics of the participating veterinary centres, their trends in small animal anaesthetic management and their perceived risks of anaesthetic-related death are described in Chapter 3. Species-specific risks of anaesthetic-related death were estimated in Chapter 4. Risk factors for anaesthetic-related death were identified in Rabbits, Dogs and Cats in Chapters 5 to 7 respectively, and additionally risk factors for dogs and cats that were already sick were studied in Chapters 6 and 7 respectively. Overall conclusions in light of the results in the different species are discussed in Chapter 8.

Chapter 1: Literature Review

1.1 Introduction

The assessment of perioperative anaesthetic complications is an important aid to maintaining and improving anaesthetic standards, and reducing morbidity and mortality. By quantifying the level of complications, it is possible to evaluate their extent and provide a benchmark from which to compare any improvements undertaken. Establishing causes and factors associated with morbidity and mortality allows for the identification of the underlying aetiology of the complication and may provide the means to improving standards. This process of critical evaluation of perioperative complications, or anaesthetic auditing, has been in place in the medical literature since the 19th century (Bunker 1986) and in the last twenty years has established the incidence of human anaesthetic mortality to be approximately 0.01 to 0.00167% (Lunn and Mushin 1982; Buck, Devlin et al. 1988; Tikkanen and Hovi-Viander 1995; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). In veterinary medicine the most recent and comparable work has been undertaken in equine anaesthesia where the death risk is nearer 1% (Johnston, Taylor et al. 1995; Johnston, Eastment et al. 2002). Small animal anaesthesia has evaluated perioperative problems, but the most comparable work is now ten to twenty years out of date (Clarke and Hall 1990; Dyson, Maxie et al. 1998). This work suggests a practice based mortality risk of nearer 0.1 %, which though better than equine anaesthesia mortality risks, leaves room for improvement. With the advent of new drugs and techniques, and improved monitoring, the need for re-evaluation of perioperative complications in small animal anaesthesia is great.

Variations in methodology in the medical and veterinary literature restrict the ease of comparison between studies within and across species. Observational studies are well suited to the study of perioperative complications; they avoid the potential ethical problems of intervention studies that may expose a study group to a potential harmful factor and often they allow the establishment of complication rates and identification of risk factors (Thrusfield 1986; Hennekens and Buring 1987; Kirkwood 1988). However they can generally only suggest underlying causes and not conclusively prove causation. Hence they are often the first major step in establishing underlying causes, but to

comprehensively establish causation intervention studies must follow (Thrusfield 1986; Hennekens and Buring 1987).

Of the possible observational study methods, some work in both the medical and veterinary literature has taken the form of case studies and series (Phillips, Frazier et al. 1960; Langley 1976; Gillick 1981; Holland 1987; Gannon 1991; Beydon, Conreux et al. 2001). These descriptive reports suggested contributory factors but to evaluate underlying causes critically, analytical studies are required. Cohort and case control studies allow the evaluation of risk factors. Cohort studies are appropriate to investigate problems with multiple outcomes and rare exposures and hence are suited to morbid studies with multiple complications (Thrusfield 1986; Hennekens and Buring 1987). Mortality, however, is a rare occurrence and under such circumstances cohort studies can be inefficient and expensive. In contrast, case-control studies are well suited to rare diseases, such as anaesthetic mortality, to multiple exposures and are generally cost efficient (Schlesselman 1982). Drawing cases and controls from a predefined cohort followed over time, i.e. a nested case-control study, can provide many of the advantages of the cohort study, with the efficiency of the case-control method, allowing risks to be documented and multiple exposures and risk factors to be assessed. This methodology has not been documented in the anaesthetic literature. The majority of work in anaesthesia has focused on cohort studies and in small animal anaesthesia, reports have generally been limited by their sample sizes and the small number of fatalities recorded (Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002). With anaesthetic mortality being rare, the use of a case-control study would be an efficient method for evaluating risk factors and the nested case-control method would additionally allow estimation of the risk of mortality.

1.2 Perioperative complication risks

Documented perioperative complication rates and risks are valuable as they indicate the likely current extent of the problem and because they provide a benchmark from which to compare subsequent work. Rates represent the number of incident cases and hence relate to a given time period. More often deaths are reported in the context of the number of anaesthetics undertaken during a specified study period, not in relation to each patient's period of time at risk, and as such the figures reported in the literature represent mortality risks. Current anaesthetic complication risks in the medical

literature, though significantly lower than those seen in veterinary medicine, are still of interest because they provide a comparative standard (Tikkanen and Hovi-Viander 1995; Eagle and Davis 1997; Suan, Perez-Torres et al. 1997; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). Large animal complication risks in contrast are higher than those seen in small animal anaesthesia (Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002). They do not provide a gold standard, but do represent patients being anaesthetised under more similar conditions to those seen in small animal anaesthesia, and hence are also a relevant comparison.

1.2.1 Morbidity versus mortality

Morbid and mortal complications have been evaluated in the medical and veterinary literature. The study of morbidity has the advantage that is likely to be more sensitive at identifying a wider range of complications and provides a broader perspective of perioperative complications. In contrast, mortal complications may only represent the tip of the iceberg and as such provides a more superficial overview.

By their nature nonfatal complications are more common and hence more efficient at generating cases. Small animal anaesthetic morbidity risks range from 2 to 10% (Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002), and thus less anaesthetic events are required to generate sufficient statistical power in a study. However the definition of a morbid anaesthetic outcome is prone to problems of misclassification. Previous work in large and small animal anaesthesia has acknowledged the difficulty of insuring consistent recording of morbid events in the practice setting (Clarke and Hall 1990; Johnston, Taylor et al. 1995; Johnston, Eastment et al. 2002). Small animal practice standards of monitoring of anaesthesia are often superficial (Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001) and unless a given complication results in obvious patient disturbance it may go unnoticed. Additionally when applied to a multi-centre study the potential for inconsistent classification of a number of morbid outcomes is more likely. Mortal complications, in contrast, are more clearly identified and classification of a single outcome increases consistency.

Evaluating multiple outcomes (e.g. multiple morbid complications) reduces the appropriateness of the case-control study (Schlesselman 1982; Hennekens and Buring 1987). Within the context of small animal anaesthetic morbidity, the application of a cohort study is appropriate (i.e. not a rare outcome), but when mortality is also to be considered (a rare outcome) a cohort study becomes an inefficient method (Schlesselman 1982; Hennekens and Buring 1987). Hence the simultaneous evaluation of both morbidity and mortality within the practice setting can prove a difficult task. Previous small animal studies that have evaluated both morbidity and mortality have often failed to evaluate both successfully: studies in which morbidity have been thoroughly considered have had insufficient statistical power to fully investigate mortality (Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002), whilst studies evaluating mortality have had limited value investigating morbidity (Clarke and Hall 1990). Given the difficulties of reliably recording morbid events (Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001) and problems of simultaneously evaluating both morbidity and mortality within the practice setting (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002), only mortality is considered in this study.

1.2.2 Considerations for comparing mortality risks

Mortality risks can vary significantly in the literature and to make an appropriate comparison between figures a number of factors must be considered. The population at risk may vary from primarily healthy patients (e.g. first opinion veterinary neutering clinics, human dental anaesthesia patients) to populations with a significant proportion of systemically ill patients (e.g. referral centres, teaching hospitals). Inevitably these differing groups of patients will have different risks of mortality. Additionally the complexity of the operations performed may vary between the populations. These clinic characteristics are likely to be reflected in mortality risks and in veterinary medicine, referral based studies will tend to higher risks than those of first opinion practices. Further, multi-centre studies will tend to reflect a broader, more heterogeneous population of patients and procedures than single centre studies and will produce mortality risks representative of a wider spectrum of anaesthetised patients. Single centre studies often were undertaken for longer periods to record larger samples and

may be prone to changes in anaesthetic practice with time.

The case definition of anaesthetic mortality varies between studies, but in general can be divided into risks where anaesthesia was the sole or primary cause of death and those where anaesthesia contributed to a multi-factorial death. The length of follow-up will also affect mortality risks. Shorter periods of follow up e.g. until regaining consciousness, are less prone to losses of follow-up but may exclude a significant group of postoperative deaths. In contrast prolonged periods of study (e.g. 30 days) may include a group of deaths without association to anaesthesia and increase the number of losses to follow-up where outcome is not recorded. Finally, the method of study may affect the accuracy of mortality risks, particularly if routinely kept records poorly document complications. If a retrospective method is adopted that relies on individuals' recall of events over 1-2 years, there could be a tendency to under reporting of deaths. This is likely to be a particular problem in veterinary practice based studies, where records are often incomplete or difficult to extract from management computer systems. In the small animal context, retrospective practice based studies in which records may be limited and information is based largely on the memory of a practitioner of an undefined outcome ('anaesthetic death') over an extended period of time (1-2 years), there could be a tendency to underestimate death risks (Dodman 1977; Dodman and Lamb 1992; Joubert 2000).

1.2.3 Human literature

In human anaesthesia, retrospective and prospective cohort studies have been undertaken for over fifty years and mortality risks have gradually decreased with time. Prospective studies are likely to record more accurate anaesthetic death risks, but where record keeping is good retrospective studies can be comparable. Of primary interest are hospital-based studies in the developed world as they generally reflect a high standard of anaesthesia care and provide a gold standard to aim for. Multi-centre studies reflect a more heterogeneous population, generally have larger sample sizes than single centre studies and should produce more representative mortality risks of anaesthetised patients in general than single –centre studies.

Singe-centre studies have been reported, though often reflect a more specific population and are limited by small numbers of patients (and deaths) and long study periods that

might reflect changing practices of anaesthesia. A single centre cohort undertaken at a UK teaching hospital published crude mortality risks of 2.9% in the early sixties, decreasing to 2.2% in the seventies (Farrow, Fowkes et al. 1982; Lunn, Farrow et al. 1982). They estimated a risk of 1 in 0.54% for patients given a good clinical assessment (approximately ASA 1-2, see Appendix 1.1). However anaesthetic and surgical causes were not distinguished, making a sensible comparison with other studies difficult.

A single-centre teaching hospital retrospective cohort study undertaken in Australia between 1963 and 1972 suggested a lower crude mortality risk of 0.2% within 24 hours of anaesthesia, decreasing to 0.059% for anaesthetic related mortality and 0.007% where anaesthesia was the sole cause of death (Bodlander 1975). Harrison, at a single-centre in South African reported death risks where anaesthesia was a significant contributory factor of 0.033% between 1956 to 1966, and 0.022% between 1967 and 1976 (Harrison 1968; Harrison 1978). Similarly, Pitt-Miller published a single-centre study of anaesthetic complications occurring over a 20 year period between 1976 and 1987 (1989). Mortality risks of 0.066% and 0.015% were reported in this study for anaesthetic-related death risks and death risks solely as a result of anaesthesia, respectively. A further single centre retrospective study undertaken in Vancouver between 1973 and 1977, suggested a similar risk of death (Turnbull, Fancourt-Smith et al. 1980). Pederson and colleagues (1990; 1994), reported an anaesthetic-related rate of 0.04% at a single centre in Sweden between 1986 and 1987. Whilst within 48 hours of anaesthesia, 0.019% patients died of a 'possibly preventable' death (Turnbull, Fancourt-Smith et al. 1980). A subsequent single-centre study reported similar anaesthetic-related death risks in South Africa between 1986 and 1987 (Coetzee and du Toit 1992). One in 2,941 (0.034%) died where anaesthesia contributed, decreasing to 0.011% of patients where anaesthesia was directly responsible (Coetzee and du Toit 1992). In contrast a 12-year study from a single hospital in the West Indies reported a comparable anaesthetic related death risk of 0.051% but a much reduced risk where anaesthesia was the sole cause of 0.002% (Pitt-Miller 1989). In Zambia, a prospective teaching hospital study was conducted in 1987 and an 'avoidable' anaesthetic death risk of 0.094%, was described (Heywood, Wilson et al. 1989). This is higher than most studies of the time and may reflect differing hospital conditions, with less monitoring and equipment and lower anaesthetist input into individual cases.

Subsequent single centre studies generally reflected lower mortality risks. At the University Hospital in Kuala Lumpur, between 1980 and 1992, a death risk primarily due to anaesthesia of 0.004% was documented (Tan and Delilkan 1993). Work in the late eighties in China also gave a lower death rate at a single hospital, where anaesthesia contributed, of 0.003% within 7 days of anaesthesia (Wu, Lai et al. 1991). A 30-year study in Japan, at a single hospital between 1962 and 1992, reported a still lower anaesthetic death risk of 0.001% (Kubota, Toyoda et al. 1994). Work at a single centre in France, between 1989 and 1995, published an anaesthetic-related mortality risk of 0.006% within 12 hours of anaesthesia (Biboulet, Aubus et al. 2001). A similar anaesthetic-related mortality risk of 0.007%, was reported in a nested case-control undertaken in a single teaching hospital in the USA between 1989 and 1999 (Newland, Ellis et al. 2002). In contrast a higher death risk of 0.015% within 24 hours of anaesthesia was reported at a Spanish hospital during 1994, where death was 'possibly associated with anaesthesia' (Suan, Perez-Torres et al. 1997). This higher risk is likely to partly reflect the more inclusive definition of anaesthetic risk. Though many of these studies were affected by factors such as their single-centre nature and limited caseload, the retrospective study method, the long study period or the crude estimation of the denominator anaesthetic numbers, generally they suggested similar orders of risk for anaesthetic related mortality and a pattern of reducing risk with time.

Multi-centre studies have reflected more varied populations at risk, though have generally confirmed similar risks that decreased with time. One of the first major multi-centre hospital based studies prospectively evaluated mortality within 10 teaching hospitals in the USA between 1948 and 1952 and documented an overall death risk of 1.33% (Beecher and Todd 1954). When the cause of death was considered, death risks of 0.064% where anaesthesia was a primary contributory cause and 0.037% where anaesthesia was directly responsible were reported. Holland reviewed anaesthetic deaths over 3 decades in New South Wales and reported decreasing numbers of deaths attributable primarily or in part to anaesthesia over the time periods (1987). Three hundred and thirty-five deaths were recorded between 1960-69, reducing to 239 between 1970 - 80 and finally to 50 deaths between 1983-85 (Holland 1987). They did not however provide denominator data and only crudely estimated the number of anaesthetics undertaken, suggesting approximate anaesthetic related mortality risks of 0.018% in 1960, 0.010% in 1970 and 0.004% in 1984. A multi-centre retrospective

cohort conducted during 1975 in Finland found a crude mortality risk within 3 days of anaesthesia of 0.180%, and an anaesthesia related mortality risk (death primarily due to anaesthesia) of 0.02% (Hovi-Viander 1980). In a follow-up study in Finland in 1986, an anaesthetic-related risk of 0.006% and a mortality risk, where anaesthesia was the main cause of death, of 0.005% were reported (Tikkanen and Hovi-Viander 1995). At a similar time (between 1978 and 1982), a national prospective multi-centre study in France published mortality risks due to cardiac arrest, within 24 hours of anaesthesia, of 0.026% where anaesthesia contributed to the death and 0.008% where the death was totally related to anaesthesia (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986).

The National Confidential Enquiry into Perioperative Deaths (National CEPOD) undertook a large scale multi-centre evaluation of perioperative complications in the UK (Lunn and Mushin 1982). An anaesthetic death risk of approximately 0.01% was identified (Lunn and Mushin 1982), where anaesthesia was the sole cause of death. Where anaesthesia contributed to the death, the mortality risk was 0.059%. The follow-up study of National CEPOD in the mid-eighties indicated an anaesthetic-related death risk of 0.084% and 0.0006% where anaesthesia was solely responsible for the death (Buck, Devlin et al. 1988). Similarly a multi-centre study in New South Wales found a mortality rate in which 'factors under the control of the anaesthetist' contributed to the death in 0.010% in the 1970's, reducing to 0.005% in the nineteen eighties (Warden, Borton et al. 1994; Warden and Horan 1996). Whilst a multi-centred randomised clinical trial of 17,000 patients in the late eighties in the USA reported 0.041% of patients died were anaesthesia 'possibly played a role' (Forrest, Cahalan et al. 1990). A study undertaken at Zimbabwean teaching hospitals in 1992 indicated an avoidable anaesthetic mortality rate of 0.033% (McKenzie 1996). This is higher than most of the reported developed world studies of the nineties and again is likely to reflect lower standards of facilities and expertise in the developing world.

Subsequently, a risk of 0.003%, where anaesthesia played a significant role, was reported in a multi-centre study in Western Australia between 1990 and 1995 (Eagle and Davis 1997). In a further multi-centre retrospective cohort conducted in the late nineties in Japan, a death risk 'totally attributable to anaesthesia' was published as 0.001% and a cardiac arrest risk 'attributable to anaesthesia' was 0.008% (Kawashima, Seo et al. 2001). In general these multi-centre studies are more likely to reflect the

risks of anaesthesia across a spectrum of patients and procedures and give a good indication of the risk of anaesthesia for a broad spectrum of patients

Dental anaesthetic studies have generally reported much lower risks of death. These risks have generally reflected the reduced risk of the patients undergoing anaesthesia and the method of collecting information on deaths, more than the standard of anaesthesia. Though arguably more similar to standards of equipment, personnel and monitoring of veterinary patients, the generally low-risk health status of the human dental population renders this a less useful comparison and standard to aim for. Lytle and Stamper (1989) reported an anaesthetic death risk of 0.0001% between 1983 and 1987 for Southern California oral and maxillo-facial surgery. This was based on a postal questionnaire relying on the recall of surgeons of complications over the previous 5 years and is likely to be an underestimate at best. Other studies have reported no deaths during their study periods (D'Eramo 1999; Matsuura, Hirose et al. 2000). Approximately 1,500,000 patients undergoing oral or maxillo-facial surgery in one of these studies reported no anaesthetic deaths, though again this was based on data from a questionnaire sent out to surgeons and is likely to underestimate the extent of complications (D'Eramo 1999). In the other study, a prospective hospital based survey, no deaths were described and this is more likely to reflect the low risk status of the patients anaesthetised and the small study size than the absolute standards of anaesthesia (13,959 anaesthetics between 1971 and 2000)(Matsuura, Hirose et al. 2000).

On the basis of both retrospective and prospective cohort studies, the anaesthetic mortality risk in man over the last decade, occurring primarily as a result of anaesthesia, was of the order of 0.050% to 0.001%, and where anaesthesia played a contributory role but was not the sole cause, was approximately 0.02% to 0.005% (Tikkanen and Hovi-Viander 1995; Eagle and Davis 1997; Suan, Perez-Torres et al. 1997; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). The distinction between death amongst healthy and sick patients has generally not been made, the nature of the operations performed has varied markedly and the nature of the populations studied has differed greatly between studies, but the overall level of complications is consistent across studies and gives a valuable estimate of the frequency of anaesthetic deaths from which to compare to veterinary studies.

1.2.4 Large animal work

Work in large animals has concentrated on equine anaesthesia complications. Studies have focused principally on referral institution populations and death risks most frequently divided into elective and emergency populations, with the latter principally representing acute abdominal or 'colic' surgery. Mitchell (1970) conducted a retrospective study at the Royal (Dick) Vet School over a seven-year period, 1962 to 1968. Four hundred and seventy three horses were anaesthetised and seven deaths occurred (death risk of 1.47%). Short at the University of Missouri, reported a smaller retrospective study of 125 horses anaesthetised with no deaths (Lumb and Jones 1973). Heath reported an overall single-clinic perioperative equine mortality risk, between 1968 and 1970, at Colorado State University of 4.35% (13 deaths out of 295 anaesthetics) (Lumb and Jones 1973). The anaesthetic death risk decreased to 1.69% when only anaesthetic related deaths were considered. In a follow up study at Colorado State University a reduced overall death risk of 1.18% was published (Lumb and Jones 1984). Many of these fatalities were due to horses undergoing emergency gastrointestinal surgery and were high-risk patients. The length of follow up was not reported in these studies so the cut off for anaesthetic related death was unclear. All of these studies were limited by their small sample size, and can only reflect crude estimates of death risks. Additionally they may represent very different populations at risk given individual centres may treat very different populations of horses.

Tevick (1983) retrospectively identified a single-clinic equine perioperative mortality risk of 2.70% over a 17-year period, reducing to 0.8% due to 'anaesthesia alone'. The majority of these deaths were within 24 hours of anaesthesia though 10 occurred after 24 hours (a period of follow-up specified as 'until the animal left the clinic'). Gastrointestinal surgery represented the major operation type in those that died and the majority of these were deemed high-risk cases. This study may have generated a larger cohort of deaths but again can only reflect the risk of a population similar to that studied. The long period of study, though helpful for producing a larger number of anaesthetics limited the value of the reported death risk. Changes in anaesthetic practice over this extended time period could have resulted in marked changes in death risks over the study period.

Further single centre reports have concentrated on vary different populations. Evaluating horses specifically undergoing colic surgery, Trim and colleagues (1988) conducted a single-clinic retrospective survey and found a perioperative death risk of 12.5% within 3 days of anaesthesia and 20% within 16 days. In contrast, a retrospective study by Young and Taylor excluded gastrointestinal surgery and reported a lower single clinic death risk over a seven-year period of 0.68% (1990; 1993). The follow-up period was not specified. More recently, Liverpool Veterinary School reported mortality risks for both elective and emergency procedures in a retrospective single clinic study (Mee, Cripps et al. 1998; Mee, Cripps et al. 1998). Of 2,276 anaesthetics, 1,279 were elective and 995 were emergency procedures. Horses were followed until discharged, for a maximum of three weeks. Of the elective anaesthetics 8 died where anaesthesia and surgery contributed to the death (0.63%) and 1 (0.078%) died solely due to anaesthesia (Mee, Cripps et al. 1998). For emergency procedures 1 in 3 died or were euthanased, with acute abdominal surgery being at increased risk (Mee, Cripps et al. 1998). For non-colic emergencies the surgical / anaesthetic death risk was 2% and for colic surgeries it was 4.35%, giving an overall emergency surgical / anaesthetic death risk of 3.85%. The overall surgical / anaesthetic death risk for elective and emergency procedures was 2%. Again the major limitation of these studies was the single centre nature of them. They represented very specific populations at risk and the mortality risks were relevant only to similar populations. Further all of the described studies were retrospective and were vulnerable to bias due to losses to follow up and may represent inaccurate estimates.

The first prospective multi-centre perioperative cohort study of equine anaesthesia, the Confidential Enquiry into Perioperative Equine Fatalities (CEPEF), was undertaken in the UK between 1991 and 1997 (Johnston, Taylor et al. 1995; Johnston, Eastment et al. 2002). Of a total of 41,824 horses anaesthetised, 39,025 were alive and 785 were dead at 7 days postoperatively giving death risks of 1.89% (Johnston, Eastment et al. 2002). When emergency abdominal surgery and delivery of foals were excluded, the death risk decreased to 0.90% (Johnston, Eastment et al. 2002). This was followed by CEPEF 3, a randomised controlled trial of 8,242 horses comparing isoflurane with halothane anaesthesia (Eastment, Johnston et al. 2002). Though representing inhalation anaesthesia only, they reported similar risks. An overall death risk of 1.61% horses and when colic and other emergency surgery were excluded a risk of approximately 0.9%

were described. In both of these studies perioperative death was defined as unexpectant death or euthanasia for perioperative complications within 7 days of anaesthesia. No attempt was made to distinguish death caused solely by anaesthesia and death occurring partly as a result of anaesthesia, and the long period of follow up potentially increased the risk of losses to follow up. Patient health status (ASA Grade) was not classified and separate death risks for sick and healthy patients were not given, though the majority of the non-colic patients were healthy. Despite these limitations the death risk for these studies covered a wide range of clinic and equine procedure types, is currently the most representative equine study and remains the benchmark from which to compare other equine studies to.

In summary, the overall anaesthetic death risks was 2.0%, decreasing amongst non-emergency horses to approximately 1.0% (Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002). Where anaesthesia was considered the sole cause of death, a risk of 0.1% was estimated (Mee, Cripps et al. 1998). Emergency anaesthetics had a death risk of nearer 1 in 10 to 30 (Trim, Adams et al. 1988; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Johnston, Eastment et al. 2002). These figures are much higher than those seen in human anaesthesia and reflect species differences as well as standards of anaesthesia.

1.2.5 Small animal work

In small animal anaesthesia, mortality risks are most comparable when the institution type and patient health statuses are considered. Referral and university-based studies generally had higher death risks due to the nature of their patients and procedures, whilst practice-based studies tend to have healthier populations, simpler procedures and lower death risks. Initial work focused on single-centre referral centre death risks (Albrecht and Blakely 1951; Lumb and Jones 1973). Work undertaken between 1946 and 1950, at the Angell Memorial Animal Hospital in Boston published an anaesthetic death risk of 0.26% in dogs, and 0.36% in cats (Albrecht and Blakely 1951). Five percent of miscellaneous species (rabbits, monkeys, etc) died perioperatively. Anaesthetic death was defined as any death occurring from the time of induction of anaesthesia until the patient returned to consciousness or his preoperative condition. The Wheatridge Animal Hospital in Colorado reported anaesthetic complications

occurring between 1960 and 1969 (Lumb and Jones 1973). Perioperative anaesthetic death risks of 0.23% in dogs (10 deaths) and 0.40% in cats (7 deaths) occurred. Anaesthetic death was defined as death interrupting recovery from anaesthesia and resulting from either sole consequence of anaesthesia, death resulting from airway obstruction while anaesthetised, or resulting from tissue damage due to inadequate oxygenation during cardiac arrest and subsequent resuscitation. The University of Missouri Veterinary Hospital reported higher mortality risks of 0.8% in dogs and 0.53% in cats between 1968 and 1969, (Lumb and Jones 1973). It is clear from these single centre studies that the definition of anaesthetic-related death varied significantly and the relevant death risks reflected very different inclusion criteria. It was less clear if the populations anaesthetised were comparable for other characteristics, such as health status, age and procedure types, and again because these were single centre studies the numbers of death reported were small in all of the studies. Hence these early studies could only give a very approximate assessment of death risks.

Colorado State University undertook a prospective cohort study of anaesthetics between 1955 and 1957 (Lumb and Jones 1973). They reported high anaesthetic death risks, of approximately 1.08% in dogs and 1.79% in cats. Anaesthetic death was defined, as 'any death occurring from the time of induction until the righting reflex returned, regardless of cause'. The high risks were attributed to students anaesthetising the majority of the cases under veterinarian supervision, the complex nature of procedures and the poor patient health status of their referral population. When healthy dogs and cats were considered (ASA 1 to 2, Appendix 1) these risks decreased to 0.65% dogs and 1.08% in cats, whilst ill dogs and cats (ASA 3 to 4) had higher death risks (5% in dogs, 10% in cats). A follow-up to this study at Colorado State University was undertaken between 1979 and 1981 (Lumb and Jones 1984). They reported improved death risks of 0.43% in dogs and 0.26% in cats of which 50% were ASA grade 1 to 2. They suggested these improvements were related to the use of safer drugs and techniques and better supervision of students undertaking anaesthesia. Subsequent to this study, they undertook a study between 1993 and 1994 (Gaynor, Dunlop et al. 1999). During this one-year period, 11 dogs (0.43%) and 3 cats (0.35%) died. Deaths included fatalities that occurred within 24 hours of anaesthesia. The health status of these fatalities was not stated.

Louisiana State University also undertook a prospective cohort study of dogs and cats at their institution between 1995 and 1996 (Hosgood and Scholl 1998; Hosgood and Scholl 2002). All dogs and cats over 6 months of age, undergoing inhalation anaesthesia for at least 30 minutes were evaluated perioperatively for up to 24 hours postoperatively. Nine hundred and forty two dogs and 138 cats were anaesthetised and 14 dogs and 8 cats died or were postoperatively euthanased within 24-hours, giving death risks of 1.49% in dogs and 5.80% in cats. These risks would be expected to be higher given that death was recorded for all patients that died within 24 hours of anaesthesia independent of cause. However the exclusion of significant strata of anaesthetised animals, namely very young patients, short inhalation anaesthetics and those receiving injectable anaesthesia only, would also have affected the reported risks. Most recently work at the Royal Veterinary College has suggested a referral centre anaesthetic related mortality risk of 0.58% in dogs (Brodbelt, Hammond et al. 2005). When healthy dogs (ASA 1-2) were considered the risk was 0.088%, whilst in sick patients (ASA 3-5) it was 1.37%. This last study emphasises the importance of reporting risks with health status, as this facilitates a broader comparison. Both these studies again reflect the limitations of single studies with small numbers of death reported and both were retrospective making them particularly susceptible to errors due to losses to follow up.

An early multi-centre cohort of practice anaesthesia evaluated feline mortality retrospectively in Scotland (Dodman 1977). A death risk of 0.312% in cats was reported, based on practitioners' recall of the number of cats that died 'as a result of anaesthesia in the last year'. This was followed by a further multi-centre retrospective cohort study of small animal anaesthetic practice, undertaken in 1989 in Vermont (Dodman and Lamb 1992). Questionnaires were sent out to 88 practitioners, 41 were returned and 39 were analysed. The average number of dogs and cats that the practitioners stated they anaesthetised each week were 15 and 16 respectively. The number they believed had 'died as a result of anaesthesia in the last two years' were 33 dogs and 19 cats, producing death risks of 0.054% and 0.029% respectively (NB the published figures are incorrect as they reported the total deaths over the two-years study period, divided by the number of anaesthetics undertaken per year). These risks are significantly lower than previous studies, but rely on practitioners' recall over a long time period and given the unclear case definition that may only refer to deaths

primarily due to anaesthesia and were likely to be an underestimate. The health statuses of the patients anaesthetised were not stated, though are likely to be 'healthier' than those reported in the referral studies, and this may reflect a component of the reported risks.

A similar retrospective study was undertaken in Finland in 1993 (Rintasalo and Vainio 1995). A questionnaire was sent to all Finnish practices and 114 centres responded. Based on the recall of practices of anaesthetic deaths (not defined) over the last 24 months, they reported a death risk of 0.126% in small animals. The most recent retrospective study evaluated complications in a South African practice population in 1999 (Joubert 2000). Six hundred questionnaires were sent out and 162 returned of which 161 were analysed. An estimated mortality risk of 0.081% in dogs and cats was recorded, though the definition of perioperative death was not stated. All these studies highlight the limitations of retrospective studies based on information derived from a single questionnaire sent out to practices. The interpretation of what constituted an anaesthetic death may have varied greatly between practices as the guidelines given were not always clear and the estimation of anaesthetics undertaken and deaths occurring was likely to be inaccurate.

The first prospective multi-centre cohort study of small animal practice complications was undertaken between 1984 and 1986 in the UK (Clarke and Hall 1990). Fifty-three practices were recruited, 41,881 anaesthetic events were recorded and anaesthetic death risks of 0.230% in dogs and 0.294% in cats were reported (48 and 59 deaths respectively). For healthy patients (ASA 1-2), the death risks were 0.115% in dogs and 0.181% in cats, whilst in ill patients (ASA 3-5), 3.13% in dogs and 3.33% in cats died perioperatively. Perioperative deaths in healthy patients (ASA 1-2), occurring during or shortly after surgery were considered 'primarily due to anaesthesia' unless an obvious surgical cause was present, whilst in sick patients all deaths were reported and no attempt was made to separate anaesthetic from other causes.

This was followed by a further prospective multi-centre cohort study of anaesthetic complications in practice in Ontario, Canada (Dyson, Maxie et al. 1998). For 6 months, 76 practices kept anaesthetic diaries of all small animal anaesthetics. Eight thousand and eighty-seven dogs and 8,702 cats were anaesthetised, with 9 and 8 perioperative deaths where anaesthesia contributed, recorded respectively. Overall perioperative

death risks were 0.111% in dogs and 0.092% in cats, and for healthy dogs and cats (ASA 1-2) they were 0.067% in dogs and 0.048% in cats. Anaesthetic related death was considered as perioperative death resulting from cardiac arrest with unsuccessful resuscitation, though the follow-up period was not specified. The number of anaesthetics and deaths recorded was relatively small, suggesting the figures could only reflect a crude approximation.

In summary, the current overall anaesthetic-related death risks in small animal practice would appear to be of the order of 0.1 – 0.2%, whilst in healthy dogs and cats the risk decreased to 0.067% to 0.050% in healthy dogs and cats and in sick patients it increased to 2 to 0.5% (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000). Current mortality risks solely due to anaesthesia were not available. In referral institutions the mortality risks were nearer 0.5% in dogs and cats, but when health status is taken into account these figures were similar to practice reports (Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002; Brodbelt, Hammond et al. 2005). Most studies were limited by their small sample sizes and the most comprehensive study undertaken to date is now nearly 20 years old (Clarke and Hall 1990). The risk of complications is lower than that seen in large animal anaesthesia, though it leaves significant room for improvement compared to human anaesthesia. The reason for these large differences is not immediately apparent but again may relate to species differences as well as variations in methodology and standards of anaesthesia.

1.3 Causes of perioperative death

Establishing mortality risks is invaluable for documenting current risks related to anaesthesia, allowing crude comparisons in standards of anaesthesia, and encouraging clinical improvement, i.e. the process of clinical audit. The investigation into the causes of these deaths allows a more complete evaluation of perioperative mortality, and when risk factors are identified, the knowledge of the major causes of death aids the understanding of potential underlying mechanisms related to these risk factors. Perioperative death may result from pre-existing disease, anaesthetic, surgical and procedural causes or a combination of all of these. Of particular relevance to a study of anaesthetic deaths are causes of death where anaesthesia contributed, but these deaths often involve procedural factors and pre-existing disease. The underlying

physiological cause may also be multi-factorial, involving the failure of a number of body systems, and when classifying a specific cause the primary precipitating aetiology is generally chosen. Cardiovascular and respiratory complications represent the major causes of perioperative deaths in the comparative and small animal literature, though gastrointestinal, neurological and hepato-renal causes have been reported. The role of human error is also relevant to causes of death, for though documentation of the primary precipitating physiological insult may direct methods to reduce fatalities in the future, documentation of the role of management errors could identify potentially important correctable problems. Reported causes of mortality were similar across the species, though the relative frequency of particular causes may be species-specific.

1.3.1 Cardiovascular causes

Cardiovascular causes form a major proportion of perioperative deaths and include cardiac pump failure and vascular collapse, resulting in failure of delivery of blood to the vital tissues. Cardiac arrest has been reported to result from cardiac arrhythmias associated with increased circulating catecholamines, myocardial hypoxia, specific anaesthetic agents, pre-existing pathology, specific procedures (e.g. vagal traction and enucleation) and with myocardial depression due to relative anaesthetic overdose (Hall and Clarke 1991; Hall and Taylor 1994). Hypovolaemia and circulatory failure are the other major cause of cardiovascular collapse and often are seen in patients with pre-existing pathology that are insufficiently stabilised prior to anaesthesia.

In human anaesthesia, cardiac arrest due to arrhythmias, myocardial depression and circulatory failure and hypovolaemia have been frequently recorded causes of death occurring in 15 to 50 % of all fatalities (Harrison 1968; Bodlander 1975; Harrison 1978; Hovi-Viander 1980; Turnbull, Fancourt-Smith et al. 1980; Tiret, Desmonts et al. 1986; Pitt-Miller 1989; Forrest, Cahalan et al. 1990; Harrison 1990; Pedersen, Eliasen et al. 1990; Wu, Lai et al. 1991; McKenzie 1996; Warden and Horan 1996; Fichtner and Dick 1997; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001).

In equine anaesthesia, cardiac arrest and cardiovascular collapse are a major cause of death, resulting in 20 to 50% of all reported deaths (Tevik 1983; Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Mee, Cripps et al. 1998; Johnston, Eastment et al. 2002). In small animal anaesthesia

cardiovascular causes also represent a major, if not more common cause. Previous studies suggest between 30 and 70% of deaths resulted from relative anaesthetic overdose and myocardial depression, cardiac arrhythmias or circulatory failure and hypovolaemia (Lumb and Jones 1984; Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Joubert 2000). Halothane, ether and thiobarbiturate anaesthesia were frequently associated with anaesthetic overdose (Clarke and Hall 1990; Dodman and Lamb 1992). Dogs more frequently had cardiovascular complications than cats in one study (Clarke and Hall 1990). High-risk patients were the most likely patients to die from circulatory failure, as they were often hypovolaemic prior to anaesthesia (Clarke and Hall 1990).

1.3.2 Respiratory causes

Respiratory complications represent the other main cause of anaesthetic-related death. Problems with airway maintenance and inadequacy of ventilation represent the principal factors resulting in death. Failed intubation, trauma to the upper airway, inadequate ventilation and delivery of a hypoxic inspired gas mixture have all been documented.

In human anaesthesia, respiratory complications have represented at least as, if not more common, a cause of death than cardiovascular causes. Inappropriate airway management and problems with endotracheal intubation caused 5 to 30% of fatalities (Bodlander 1975; Buck, Devlin et al. 1988; Caplan, Posner et al. 1990; Harrison 1990; Gannon 1991; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). Inadequate ventilation has been the cause in 15 to 40% of reported deaths (Harrison 1978; Hovi-Viander 1980; Holland 1987; Caplan, Posner et al. 1990; Harrison 1990; McKenzie 1996; Fichtner and Dick 1997). Additionally the supply of a hypoxic gas mixture, and development of pneumothorax have been reported (Holland 1987; Gannon 1991). Hence, overall respiratory causes have represented 20 to 50% of all anaesthetic deaths (Harrison 1968; Harrison 1978; Hovi-Viander 1980; Turnbull, Fancourt-Smith et al. 1980; Tiret, Desmonts et al. 1986; Holland 1987; Heywood, Wilson et al. 1989; Pitt-Miller 1989; Caplan, Posner et al. 1990; Forrest, Cahalan et al. 1990; Harrison 1990; Pedersen, Eliasen et al. 1990; Gannon 1991; McKenzie 1996; Warden and Horan 1996; Fichtner and Dick 1997; Kawashima, Seo et al. 2001)

In contrast, equine anaesthetic fatalities have infrequently been due to respiratory complications. Though Tevik (1983) did not distinguish respiratory from cardiovascular causes, which when combined accounted for all 10 anaesthetic deaths described, other studies have reported less than 25% of all deaths resulted from respiratory compromise (Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Mee, Cripps et al. 1998; Johnston, Eastment et al. 2002). Johnston and colleagues' (1995; 2002) multi-centre study documented only 4% of deaths resulted from respiratory problems.

Respiratory complications were an underlying cause of death in 30 - 40% of dogs and about 40 - 50% of cats (Lumb and Jones 1984; Clarke and Hall 1990; Dyson, Maxie et al. 1998). Endotracheal intubation problems and respiratory obstruction represented the majority of feline respiratory causes of death (Clarke and Hall 1990; Dyson, Maxie et al. 1998). In dogs, complications with endotracheal intubation and respiratory failure were equally reported, though in brachycephalic dogs respiratory obstruction was the principal cause of respiratory complications (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998).

1.3.3 Miscellaneous causes of death

Other causes of perioperative death include inhalation of gastric contents, sepsis, shock and multiple organ failure, renal failure, failure to regain consciousness and rarely anaphylactic reactions to the fluids or anaesthetics administered.

In the medical literature, these causes have been infrequently documented. Up to 20% of all deaths were attributed to shock, sepsis and multi-organ failure and generally these deaths were seen in the patients that presented for anaesthesia with systemic illness (Heywood, Wilson et al. 1989; Pitt-Miller 1989; McKenzie 1996; Fichtner and Dick 1997). Other causes reported in the human literature included anaphylactic reactions to intravenous colloids and blood transfusions, allergic bronchospasm, pulmonary embolism, inhalation of gastric contents, renal and hepatic failure and equipment failure (Harrison 1968; Bodlander 1975; Harrison 1978; Hovi-Viander 1980; Turnbull, Fancourt-Smith et al. 1980; Tiret, Desmonts et al. 1986; Holland 1987; Heywood, Wilson et al. 1989; Pitt-Miller 1989; Harrison 1990; Pedersen, Eliasen et al. 1990; Gannon 1991; Warden, Borton et al. 1994; McKenzie 1996; Warden and Horan

1996; Beydon, Conreux et al. 2001). This is in contrast to the causes of death in horses. Non-cardiopulmonary causes have been reported as the cause of death or euthanasia in up to 77% of all equine fatalities (Tevik 1983; Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Mee, Cripps et al. 1998; Mee, Cripps et al. 1998; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002). Johnston and colleagues (1995; 2002) attributed death in 55% of all cases to fractures on recovery, postoperative myopathy and abdominal complication such as sepsis and colitis. Young and Taylor (1993) reported deaths due to postoperative myopathy and fractures in 7 of 9 deaths. Rarely have horses been reported 'found dead' or dying of unknown cause, with Johnston and colleagues indicating only 5% being 'found dead' (2002).

In small animal anaesthesia, causes other than respiratory and cardiovascular complications have infrequently been reported, though have included postoperative renal failure, iliac thrombosis in cats, gastric contents inhalation, anaphylactic reactions, failure to regain consciousness and of unknown cause (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000). The latter cause, often arising when patients were not being closely watched, represented approximately 5 to 20 % of patients. Generally these non-pulmonary causes were more similar to those reported in the human literature, though the failure to regain consciousness and unknown cause may reflect a difference in the standards of monitoring and critical care medicine rather than specific species differences.

1.3.4 The role of human error

In the medical literature a major focus has been the identification of the role of the anaesthetist in fatalities. The report of the Confidential Enquiry into Perioperative Deaths (Buck, Devlin et al. 1988) documented human errors of insufficient knowledge, failure to apply this knowledge, lack of care in patient management and inexperience as major factors in over 75% of anaesthetic-associated deaths. Similarly, other studies have reported approximately two thirds of anaesthetic-related deaths being due to anaesthetic management deficiencies (Utting 1987; Caplan, Posner et al. 1990; Gannon 1991). The majority of these errors resulted from problems with patient airway management and endotracheal intubation and ventilation (Tiret, Desmonts et al. 1986; Holland 1987; Buck, Devlin et al. 1988; Caplan, Posner et al. 1990; Harrison 1990; Gannon 1991; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). In the veterinary literature

infrequently has the human error element of deaths been quantified. In small animals, Clarke and Hall (1990) documented errors of patient management in over 75% of deaths in healthy (ASA 1-2) dogs and cats and again the majority related to airway complications during anaesthesia, though in other studies the role of error has not been reported. Identifying the human element of anaesthetic-related deaths is relevant to improving standards as it can target recurrent weaknesses in patient management that could reduce complications if corrected, in addition to the value of documenting the major body systems most frequently affected by anaesthesia. Further, identifying human error may help account for some unexpected associations found, and provide a reasonable alternative explanation for specific associations linking anaesthetic technique and outcome.

In summary, the range of causes of death was approximately similar across species and focused on cardiovascular and respiratory complications. Species-specific differences were present with human and possibly feline patients more likely to die of respiratory than cardiovascular causes, dogs of cardiovascular causes and horses rarely of pulmonary causes (Bodlander 1975; Hovi-Viander 1980; Tevik 1983; Buck, Devlin et al. 1988; Caplan, Posner et al. 1990; Clarke and Hall 1990; Harrison 1990; Dodman and Lamb 1992; Young and Taylor 1993; Johnston, Taylor et al. 1995; Fichtner and Dick 1997; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Mee, Cripps et al. 1998; Mee, Cripps et al. 1998; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001; Johnston, Eastment et al. 2002). The role of human error in these deaths was documented in many of the medical studies (Tiret, Desmonts et al. 1986; Holland 1987; Buck, Devlin et al. 1988; Caplan, Posner et al. 1990; Harrison 1990; Gannon 1991; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001) but only rarely in the veterinary literature (Clarke and Hall 1990). The combination of an understanding of the physiological basis of fatalities and the role of human management in these deaths can form in invaluable platform from which to assess anaesthetic deaths and focus priorities in the improvement of anaesthetic practice.

1.4 Risk factors for mortality

Identifying risk factors associated with anaesthetic mortality is valuable if changes in anaesthetic practice and reduction in complications are to occur. Factors reported to be associated with death in the medical literature are relevant as the underlying

mechanisms and deficiencies in clinical practice are likely to be similar to those seen in veterinary anaesthesia. Risk factors identified in large animal anaesthesia are also informative both because of the species similarities and because the practice of anaesthesia in other veterinary species will generally be more comparable to small animal than human anaesthesia.

1.4.1 Human literature

Early case reports and cohort studies evaluated possible causes of death and suggested possible contributory factors, but did not investigate risk factors *per se* (Phillips, Frazier et al. 1960; Hovi-Viander 1980; Holland 1987; Tinker, Dull et al. 1989; Caplan, Posner et al. 1990; Gannon 1991; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Eagle and Davis 1997; Suan, Perez-Torres et al. 1997; Beydon, Conreux et al. 2001). Subsequent studies have attempted to address risk factors within the framework of cohort and case-control studies, though many of these studies reported risks for specific factors without comparing them to a baseline of risk, were unadjusted for other factors and as such could provide only crude assessments of factors (Beecher and Todd 1954; Farrow, Fowkes et al. 1982; Lunn and Mushin 1982; Buck, Devlin et al. 1988; Heywood, Wilson et al. 1989; Campling, Devlin et al. 1990; Campling, Devlin et al. 1992; Campling, Devlin et al. 1993; Warden, Borton et al. 1994; Warden and Horan 1996; Biboulet, Aubus et al. 2001; Iwao, Kawashima et al. 2001; Morita, Kawashima et al. 2001; Irita, Kawashima et al. 2002). More recently a number of studies have been able to quantify risk associated with specific factors, reporting odds or risk ratios and additionally some have adjusted for other risk factors or undertaken more detailed statistical analysis (Fowkes, Lunn et al. 1982; Farrow, Fowkes et al. 1984; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Pedersen, Eliasen et al. 1990; Pedersen 1994; Howell, Sear et al. 1998; Howell, Sear et al. 1999; Newland, Ellis et al. 2002). Few intervention studies have been published and often they were limited by sample size, however one study was able to study a large population and apply more comprehensive statistical analysis (Forrest, Rehder et al. 1992).

An early case series suggested increased risk associated with chloroform anaesthesia (Phillips, Frazier et al. 1960). Holland (1987) in a retrospective study of anaesthetic deaths over thirty years attributed death to poor preparation, incorrect anaesthetic selection and dosing, poor monitoring, poor maintenance of oxygenation and

ventilation and poor perioperative and crisis management, though they did not quantify the risk associated with these factors. Work in Finland (Hovi-Viander 1980; Tikkanen and Hovi-Viander 1995) suggested poor patient preparation, poor patient health status and old age contributed to anaesthetic death though again they did not assess the magnitude of these risks. Tinker and colleagues (1989) when analysing 1,175 anaesthetic related closed malpractice claims in the USA, identified the lack of pulse oximetry and capnometry as major contributory factors. In a further closed claims series of 522 adverse respiratory events (of which 85% of incidents resulted in death or brain damage), problems of inadequate ventilation and trouble with intubation were major factors and poor monitoring was thought likely to contribute to the complication (Caplan, Posner et al. 1990). A review of 25 anaesthetic deaths reported in the UK highlighted contributory factors of poor communication, inadequate preoperative assessment and preparation and times periods when the anaesthetist was not present (Gannon 1991). A multi-centre Zimbabwean study also identified common characteristics of anaesthetic deaths, including surgeon and anaesthetist inexperience, procedure type, patient age, and patient sex, but no denominator data on the frequencies of these factors in the non-fatalities, were reported and the authors were only able to speculate on the likelihood of these factors being risk factors for death (McKenzie 1996). Similarly an Australian study (Eagle and Davis 1997) and a Spanish report (Suan, Perez-Torres et al. 1997) documented similar features of the anaesthetic deaths but neither had data on non-deaths to identify risk factors with. More recently in France, an analysis of 1004 serious incidents, including mortality, where equipment failure contributed to the complication, was undertaken (Beydon, Conreux et al. 2001). Failure of ventilation, infusion and monitoring equipment constituted the majority of these failures. None of these studies was able to quantify risk in the context of a given exposure or outcome, but they did provide a starting point and identified a number of factors potentially contributing to anaesthetic death, including inadequate monitoring, poor anaesthetic equipment function, poor preoperative management and poor communication, surgeon and anaesthetist inexperience, patient old age, and poor health status.

Subsequent studies reported similar and additional risk factors but also attempted to quantify the risk of death associated with specific factors. Many of these studies did not however attempt statistical analysis or adjust for other risk factors or confounders.

Beecher and Todd in their prospective study (1954) identified the use of the neuromuscular blocking agent, curare, as a major risk factor and reported mortality risks for other factors suggesting increased risk with ether, cyclopropane, nitrous oxide, thiopentone, and regional anaesthesia. They did not however report relative risks, undertake statistical analysis or attempt to adjust these factors for other exposure variables, with the exception of stratifying the risk with curare on health status (Beecher and Todd 1954). Early prospective work undertaken in the UK also identified increased risk of death with old age, patient sex, preoperative clinical disease and health status, surgical type, site and urgency and duration of anaesthesia (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982). These studies identified mortality rates for patients with specific exposures, though only published risk ratios for major coexisting diseases, and they did not undertake further statistical analysis.

The National Confidential Enquiry into Perioperative Deaths (National CEPOD) identified a number of risk factors within the setting of a national UK survey (Lunn and Mushin 1982). Factors identified as contributing to death included poor supervision of trainee anaesthetists, inadequate monitoring, pre-existing disease, old age, urgency of operation and poor recovery facilities (Lunn and Mushin 1982; Buck, Devlin et al. 1988). However they did not statistically evaluate the risk of these factors or adjust for confounders. Later reports of the National CEPOD have effectively been case-control studies (Campling, Devlin et al. 1990; Campling, Devlin et al. 1992; Campling, Devlin et al. 1993). They compared twenty percent of all anaesthetic deaths, to 'index' anaesthetics drawn from operations undertaken on a specified date or from a specified list of operations. Matched controls were requested from participating hospitals but were eventually abandoned as insufficient numbers were received (Campling, Devlin et al. 1992). There was a tendency to increased risk of death with pre-existing disease and therapy, and poor monitoring of the anaesthetised patient, whilst reduced risk was seen when premedication was given (Campling, Devlin et al. 1992; Campling, Devlin et al. 1993). Again they did not calculate odds ratios or attempt statistical analysis, but they did publish the number of deaths and index controls with their respective exposure statuses, so odds ratios could be calculated.

Work in Zambia identified emergency status, old age, patient sex and anaesthetist experience as risk factors, and allowed comparisons of risk associated with these

factors, though the authors did not attempt statistical analysis or adjust for multiple factors (Heywood, Wilson et al. 1989). Warden and colleagues reported on causes of death in an Australian study undertaken between 1984 and 1990, and found cardiovascular and vascular surgery to carry the highest risk, males to be at greater risk, and old age to be at increased risk (Warden, Borton et al. 1994; Warden and Horan 1996). They did not quantify the relative risks, though this information was available in their published report, and they did not statistically evaluate differences or assess multiple factors. Prospective work in France identified old age, poor health status as described by the ASA health status classification (see appendix 1), pre-existing disease, specific procedure type, emergency procedures, long operation time, and the type of hospital (teaching, non-teaching or private) as factors associated with anaesthetic-related cardiac arrest (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986). They reported relative risks and in the later study compared these single variable relative risks statistically, finding significant differences for these risk factors (Tiret, Desmonts et al. 1986). Certain factors were graphically stratified on age or health status, but they did not attempt more detailed analysis. A subsequent French study also evaluated risk factors and reported mortality risks for specific factors, similarly identifying old age, increasingly poor health status (ASA grade), regional versus general anaesthesia and emergency operations, but this study also did not statistically assess risk factors or adjust for multiple factors (Biboulet, Aubus et al. 2001). A Japanese study undertaken in 1999, also identified health status (ASA grade) and age as risk factors (Iwao, Kawashima et al. 2001; Morita, Kawashima et al. 2001; Irita, Kawashima et al. 2002). Interestingly intravenous anaesthesia was associated with a higher risk of death than inhalational anaesthesia, though only risks of death in each subpopulation were reported, and no statistical analysis or adjustment for confounding factors was undertaken (Seo, Kawashima et al. 2001).

Other studies have attempted to more thoroughly assess risk factors. A Danish prospective cohort studied 7,000 patients at a single hospital and used regression analysis to develop a model of mortal risk (Pedersen, Eliasen et al. 1990; Pedersen 1994). Increasing patient age, history of heart disease, pulmonary disease, renal disease, emergency surgery, and abdominal surgery were all associated with increased risk. However the power of the study was limited by the small sample size.

A matched case-control study of risk factors for cardiovascular death of elective and emergency procedures was undertaken over a 12-year period in the nineteen-eighties (Howell, Sear et al. 1998; Howell, Sear et al. 1999). Using multivariable analysis they identified pre-existing myocardial infarction, hypertension and renal failure as the main risk factors for cardiovascular death in elective procedures and a history of cardiac failure in emergency operations (Howell, Sear et al. 1998; Howell, Sear et al. 1999). They did not however evaluate exposure variables other than pre-existing diseases. A multi-centre randomised clinical trial of the safety of 4 anaesthetic protocols suggested increased risk of severe outcome including death, with pre-existing cardiac failure, myocardial ischaemia or hypertension, poor health status, old age, and cardiovascular, thoracic or abdominal surgery, though they could find no significant differences between anaesthetic agents used when assessing risk of death (Forrest, Cahalan et al. 1990; Forrest, Rehder et al. 1992). These results were based on logistic regression analysis with a number of serious outcome variables, and though they were able to identify major risk factors they had insufficient deaths to evaluate many factors associated with a fatal outcome (Forrest, Cahalan et al. 1990; Forrest, Rehder et al. 1992).

Newland and colleagues (2002) undertook a nested case-control, over a 10-year period between 1989 and 1999, of anaesthetic-related cardiac arrests within 24 hours of anaesthesia. At the univariable stage old age, poor health status, emergency surgery, thoracic, spinal or abdominal surgery, afternoon surgery and long operation time were associated with increased risk of cardiac arrest. When adjusting for other factors only heath status, surgical type and emergency surgery remained in the model. Again, the power of this study was limited by its' small number of cases. Only 15 cardiac arrests were deemed to be anaesthetic-related. Similarly, a recent prospective multi-centre cohort study identified health status, age, procedure urgency and complexity (minor, moderate or major) as risk factors and predictors of operative risk within a logistic regression model (Donati, Ruzzi et al. 2004). It also had only moderate power with 38 deaths being recorded during the study period, and thus could only identify major risk factors. Thus these latter studies more comprehensively evaluated risk factors, though they still did not have sufficient numbers of anaesthetic-related deaths to evaluate more than a few central risk factors.

In summary, factors associated with anaesthetic death in the medical literature include pre-existing disease and poor health status, old age, long or urgent procedures, thoracic and abdominal surgery, anaesthetist and surgeon inexperience, poor patient management and insufficient monitoring. Risks associated with specific drugs have not been thoroughly evaluated, and only in a few reports have specific risk factors been quantified and adjusted for confounding variables. Later studies have employed more advanced statistical tools including logistic regression to evaluate multiple factors though they have generally been restricted by their small numbers of fatalities to evaluating only a few central factors including old age, poor health status, surgery urgency and location of surgery. Nonetheless these medical reports do highlight a number of factors potentially relevant to veterinary anaesthesia.

1.4.2 Large animal work

Severe complications causing death or necessitating euthanasia have been reported in case reports in the equine literature and causes of death have been hypothesized (Blakemore, Jefferies et al. 1984; Brearley, Jones et al. 1986; Klein, Ailes et al. 1989; Dixon, Railiton et al. 1993; Peek 1993; Lam, Smyth et al. 1995; Mackay, Forest et al. 2002). However such work did not specifically address risk factors and could only form the basis of hypotheses of contributory factors to study further in analytical studies (Schlesselman 1982; Thrusfield 1986; Hennekens and Buring 1987).

A number of single-centre retrospective studies have identified risk factors associated with perioperative complications in horses. In studies undertaken at Colorado State University postoperative myopathy and anaesthetic overdose were major causes of death or euthanasia, and many of these fatalities were associated with emergency gastrointestinal surgery and high-risk status (Lumb and Jones 1973; Lumb and Jones 1984). Tevick (1983) identified gastrointestinal surgery as the principal operation type in those horses that died and the majority of these were deemed high-risk cases. Statistical analysis was not performed on these data. However, amongst horses undergoing acute emergency abdominal surgery, long duration of anaesthesia and intraoperative hypotension were associated with increased risk of death in a further single centre retrospective study (Trim, Adams et al. 1988).

Interestingly, when factors were evaluated in non-colic horses, similar risk factors were identified (Young and Taylor 1990; Young and Taylor 1993). Intraoperative fluids and positive inotropic support were associated with reduced risk of fatal myopathy, whilst long procedures and old age were associated with increased risk of death or myopathy. Subsequent work evaluated both elective and emergency procedures in a further retrospective single clinic study (Mee, Cripps et al. 1998; Mee, Cripps et al. 1998). High ASA grade in the elective cases was associated with increased risk of death, and amongst emergency patients acute abdominal surgery ('colic' surgery) was at increased risk. Only limited statistical analysis was undertaken with no adjustment for confounding variables other than stratification into elective and emergency cases in the latter study, and all of these single-centre studies had insufficient statistical power to look at more than a small number of exposure variables adequately.

The prospective multi-centre cohort undertaken by Johnston and colleagues (1995; 2002) evaluated risk factors more thoroughly, calculating odds ratios and using logistic regression to adjust for confounding factors. They identified anaesthesia of pregnant mares and foals, horses undergoing abdominal surgery, orthopaedics requiring internal fixation, long operation time, positioning in dorsal recumbency, lack of sedation and the use of xylazine as a premedicant with increased risk. Acepromazine premedication and total intravenous anaesthesia were associated with reduced risk. They excluded colic surgery and caesarean section from the analysis of risk factors, a potentially important group to study. Further, health status was not recorded, and though the majority of non-colics and non-caesarean section horses would have been healthy, this was not established and could not be adjusted for in the final model. The subsequent phase of the work, a randomised clinical trial of isoflurane and halothane for maintenance of anaesthesia did record the horses' health statuses (Eastment, Johnston et al. 2002). In general, no difference in outcome between the two anaesthetics was found, but in horses aged 2 – 5, isoflurane was associated with reduced odds. In both treatment groups increased risk was seen with orthopaedic and emergency abdominal surgery whilst reduced risk occurred with monitoring of blood pressure, and with ear, nose and throat and uro-genital surgery.

This multi-centre recent work has been uniquely able to quantify specific risk factors and drug associations (Johnston, Taylor et al. 1995; Eastment, Johnston et al. 2002;

Johnston, Eastment et al. 2002), but the patterns are similar to those reported in the other equine studies. The work in equine anaesthesia indicates risk factors similar to those published in the medical literature. In particular emergency, abdominal and orthopaedic surgery, long operations, poor health status, and extremes of age were commonly reported factors associated with death. In addition, risks associated with specific anaesthetic agents have been addressed and lack of sedation, and xylazine administration were associated with increased risk whilst acepromazine premedication, total intravenous anaesthesia, isoflurane in 2-5 year old horses and blood pressure monitoring were associated with reduced risk. Though these factors relate to a different species they are valuable, for whereas the medical literature has generally avoided or been unable to evaluate anaesthetic agents, the later studies in equine anaesthesia have addressed commonly used drugs. The risk associated with these drugs provides support for possible hypothesised risk factors in small animal anaesthesia.

1.4.3 Small animal work

Initial work took the form of case reports. Adverse reactions occurring in practice were reported as case series and the use of high doses of acepromazine and concentrated solutions of thiopentone (5%) were associated with fatalities (Langley 1976). Gillick (1981) reported frequent complications in Canada with specific drug combinations. He stated that increased numbers of complaints were received from clients of dogs and cats dying after xylazine (an $alpha_2$ adrenoceptor agonists) and ketamine anaesthesia. These early reports could give no indication of the extent of the problem, but identified possible hypotheses, including increased risk with $alpha_2$ adrenoceptor agonists, and provided stimulus for further studies.

Early single institution retrospective studies suggested contributory factors without being able to provide in-depth analysis (Albrecht and Blakely 1951; Lumb and Jones 1973). The use of ether and pentobarbital in dogs and cats was associated with higher mortality, and trauma patients, neutering procedures, brachycephalic and fox terrier breeds were frequently represented amongst the fatalities. However, without denominator data on the frequency of these factors in the anaesthetised population, it could not be determined if the increased number of deaths reflects increased risk or commonly occurring exposure factors. A study at the Wheatridge Animal Hospital

suggested increased risk of death with extremes of age, though no quantification of risk was undertaken (Lumb and Jones 1973).

Work at Colorado State University between 1955 and 1957 identified higher death risks in cocker spaniels, in spayed versus non-spayed female patients, and for animals undergoing ovariohysterectomy (Lumb and Jones 1973). Anaesthetist error was a contributory factor in a number of the deaths, and the recovery period was associated with the greatest perioperative risk. Ether was associated with higher death risks, whilst injectable anaesthesia and halothane (dogs only) were associated with lower death risks. They expressed risk of death associated with each factor per number of anaesthetised patients receiving that factor and stratified the results on health status (ASA grade), though no statistical analysis was performed. A follow-up study undertaken between 1979 and 1981 found no breed predisposition, anaesthetic overdose was a common problem, and endotracheal tube complications were reported (Lumb and Jones 1984). However neither this study, nor their subsequent report undertaken at Colorado State during 1993 to 1994 (Gaynor, Dunlop et al. 1999), quantified the risks associated with specific factors or adjusted for confounding variables and all three studies were limited by their small sample size and single-centre nature representative only of a specific referral population.

A prospective cohort study undertaken at Louisiana State University evaluated risk factors and calculated adjusted odds ratios (OR) using regression analysis (Hosgood and Scholl 1998; Hosgood and Scholl 2002). Increased risk of serious perioperative complication (including death) was associated with old age in dogs (OR = 2) and high-risk status in dogs and cats (ASA 3-5; dogs OR = 3.9, cats relative risk 3.9), whilst anaesthetic time and surgery type were not associated with risk. These studies were limited by their small sample size, particularly in the study of cat complications (Hosgood and Scholl 2002), in which only 9 deaths were reported.

A recent study of perioperative canine complications at the Royal Veterinary College confirmed the relevance of health status as a risk factor (Brodbelt, Hammond et al. 2005). They undertook a nested case-control study, and found that high-risk status was associated with an increased risk (OR = 28.5), whilst acepromazine with reduced risk (OR = 0.1). All these studies were limited by their small sample sizes, and their ability to look at more than a small number of variables was limited. They illustrated the

difficulty of generating sufficient cases and statistical power from single-centre studies. Additionally they reflected a higher risk population than practice based studies and the risk factors identified might not be relevant to a practice based population.

An early practice-based study of feline anaesthesia was unable to fully address risk factors, but identified a trend to reduced risk with thiopentone/halothane anaesthesia relative to other drugs (Dodman 1977). A retrospective practice based study undertaken in Vermont by Dodman and Lamb (1992) also did not evaluate risk factors but did identify high risk with xylazine administration and brachycephalic breeds. Hence these early reports provided some support for risk factors in practice populations but like many of the institution based studies did not quantify risk.

The first major prospective multi-centre practice based study, investigated risk factors associated with death (Clarke and Hall 1990). They estimated death risks in healthy dogs and cats (ASA 1-2) associated with specific risk factors, though did not compare risks relative to baseline and statistical analyses were not performed. Higher death risks were seen in healthy dogs and cats with xylazine use. In cats, endotracheal intubation, volatile induction of anaesthesia, thiopentone, methohexitone, ketamine, halothane, ether and nitrous oxide use were also associated with higher death risks. In dogs, Pekingese were the most commonly reported breed to die. Reduced death risks were associated with atropine and acepromazine premedication in both dogs and cats. Saffan administration in cats, and halothane and thiopentone use in dogs were also associated with lower death risks. In the ill dogs and cats (ASA 3-5), pre-existing disease commonly contributed to death, though in neither species was it possible to investigate risk factors further. The lack of statistical analysis limited this study and the inability to adjust for confounders requires the data to be interpreted cautiously. Nonetheless the major confounder was likely to be health status and they did stratify the results by reporting the results of the healthy stratum separate to those of the sick patients. The systematic analysis of every 10^{th} page of the cohort diary entries when recording the exposure variables of the anaesthetised population could have predisposed to errors of bias, though the clinical significance of this was likely to be small. The study is now nearly 20 years old and with the advent of new anaesthetic agents, improved monitoring and anaesthetic techniques, the direct application of these results to the modern small

animal anaesthetic population was limited. However this remains the most comprehensive study to date and the only major study conducted in the UK.

The practice based cohort study of anaesthetic complications in Ontario did calculate odds ratios for morbidity and mortality and apply logistic regression to adjust for multiple factors and construct a model for perioperative cardiac arrest (Dyson, Maxie et al. 1998). They concentrated on morbid outcomes and did not have sufficient deaths to thoroughly evaluate risk factors for death. Nonetheless increased odds ratios for perioperative cardiac arrest, were found for dogs given xylazine (OR = 43.6) and for sick patients (ASA 3-5, OR = 7). In cats, sick patients (ASA 3-5) were at greater risk of death (OR = 21.6), whilst the presence of a technician monitoring the anaesthetic reduced risk (OR = 0.19).

In summary, only the later studies have critically evaluated risk factor for death (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Hosgood and Scholl 2002; Brodbelt, Hammond et al. 2005). Commonly reported risk factors for death are similar to those seen in the medical and equine literature and include poor health status, old age, and poor monitoring. Interestingly the risks associated with xylazine and acepromazine appear similar to those reported in large animals, and intubation of cats appears a high-risk procedure. The majority of these studies have been limited by their sample sizes when attempting to assess a number of risk factors and to adjust for potential confounders. Only the more recent practice based multi-centre studies have been able to look more thoroughly at a range of risk factors, but even these are now 10 to 20 years old (Clarke and Hall 1990; Dyson, Maxie et al. 1998).

1.4.4 Biological bases of risk factors

Previous studies have highlighted a number of risk factors for anaesthetic death. Given the knowledge of likely causes of perioperative death it is possible to suggest mechanisms by which the risk factors contribute to mortality. Establishing causation with respect to given risk factors is difficult however within the context of an observational study. When viewed in the light of postulated mechanisms of action of these risk factors combined with published experimental studies supporting these mechanisms, a greater body of evidence for a causative association between exposure factor and outcome is possible (Schlesselman 1982; Thrusfield 1986; Hennekens and

Buring 1987). Hence an understanding of the likely mechanisms of action of risk factors in contributing to death is useful when evaluating the biological plausibility of an association (Hill 1965).

1.4.4.1 Patient related risk factors

The presence of pre-existing disease has consistently been reported as a risk factor for anaesthetic death (Lumb and Jones 1984; Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Hosgood and Scholl 2002; Brodbelt, Hammond et al. 2005). This is not surprising given that disturbance of major body systems will make the patient less tolerant of physiological depression induced by anaesthesia. Pre-existing cardiopulmonary pathology is particularly relevant in the immediate perioperative period, as anaesthetic-related mortality is likely to involve respiratory or cardiovascular compromise, and most anaesthetics depress one or both systems at clinical levels of anaesthesia (Hall and Clarke 1991; Hall and Taylor 1994). This pathology may reduce the therapeutic index of administered anaesthetics and increase the potential for relative overdose.

Haematological and biochemical abnormalities may also be significant. In particular, anaemia will reduce oxygen carrying capacity and predispose to hypoxia, whilst hypoproteinaemia may increase the sensitivity of the patient to highly protein bound drugs, and result in relative overdose (Hall and Clarke 1991). Renal disease is also important, particularly if dehydration or uraemia is present, as under these conditions the kidneys will have a lower tolerance to anaesthesia and the patient will be more sensitive to anaesthetics given. After hypotensive anaesthesia, chronic renal failure may be converted to acute disease (Hall and Clarke 1991). Neurological disease may be relevant with respect to the occurrence of postoperative seizures, increased sensitivity to anaesthetics and when cardiopulmonary function is affected, e.g. medullary pathology can depress ventilation and cardiovascular function. Additionally liver and endocrine disease may influence the response to anaesthesia, with diabetes mellitus and potential intraoperative cellular hypoglycaemia being particularly relevant (Johnson 1999).

Brachycephalic breeds have been found to be at greater risk (Lumb and Jones 1973; Clarke and Hall 1990; Dodman and Lamb 1992). When sedated or anaesthetised redundant pharyngeal tissue may partially obstruct their upper airway; when this is

combined with the breeds' tendency to narrow tracheas, stenotic nares and prolonged soft palates, significant airway obstruction may result (Hall and Clarke 1991; Thurmon, Tranquilli et al. 1996) Additionally, some breeds (e.g. boxers) are particularly sensitive to the vasodilatatory effects of the phenothiazines (Hall and Clarke 1991).

Age has been reported in some studies to be a significant risk factor in dogs but not cats (Hosgood and Scholl 1998; Hosgood and Scholl 2002), though other studies have been unable to find an association in either (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Brodbelt, Hammond et al. 2005). Greater risk for the extremities of age would be expected. Young animals have higher surface area to volume ratios and are physiologically immature making them less tolerant of anaesthetic effects and more prone to hypothermia and delayed recoveries. Older patients tend to have reduced cardiopulmonary, and renal reserves making them more prone to the depressant effects of anaesthesia (Meyer 1999).

1.4.4.2 Procedure related risk factors

Increased risk has been associated with emergency procedures in the human and equine literature (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002) though not in small animal studies. The risk is likely to reflect the combined effect of the nature and urgency of the operation, the health status of the patient and the inability to stabilise the patient preoperatively. Procedure duration has also been reported as a risk factor in the comparative literature (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Trim, Adams et al. 1988; Young and Taylor 1990; Young and Taylor 1993; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002) and this may again reflect the difficulty of the procedure as well as time dependent effects of anaesthesia. Prolonged anaesthesia predisposes to hypothermia, which can induce cardiopulmonary depression and reduce drug metabolism, additional to that induced by the anaesthetic agents used (Waterman 1981; Dhupa 1995).

1.4.4.3 Anaesthetic risk factors

Xylazine, an alpha$_2$ adrenoceptor agonist, was associated with increased risk in a number of veterinary studies (Gillick 1981; Clarke and Hall 1990; Johnston, Taylor et al. 1995; Dyson, Maxie et al. 1998). The physiological effects of the alpha$_2$ agonists are well known and include transient hypertension followed by hypotension, bradycardia, increased systemic vascular resistance and reduced cardiac output (Muir 1977; Greene and Tranquilli 1988; Savola 1989; Wagner, Muir et al. 1991; Cullen 1996; Ko, Bailey et al. 1996; Golden, Bright et al. 1998; Pyendop and Verstegen 1998; Pyendop and Verstegen 1999). Additionally, xylazine has been found to sensitise the heart to catecholamine-induced arrhythmias under halothane anaesthesia (Muir, Werner et al. 1975; Tranquilli, Thurmon et al. 1986) or a least not increase the threshold to these arrhythmias (Lemke, Tranquilli et al. 1993; Dyson and Pettifer 1997). Ventilation is generally preserved or only mild respiratory depression is seen (Bloor, Abdul-Rasool et al. 1989; Pyendop and Verstegen 1999).

Clarke and Hall (1990) concluded that the majority of the complications with xylazine were associated with lack of familiarity with the agent and the use of relatively high doses. Given the cardiovascular effects and slowing of the circulation seen with the alpha$_2$ adrenoceptor agonists, the effects of subsequently administered anaesthetic agents will be delayed. If an induction agent is not given slowly to effect at a significantly reduced dose (relative to the dose when an alpha$_2$ agonist is not used), the potential for relative overdose is real. Nonetheless, the cardiovascular effects are dramatic and these alone may play a significant role. The tendency of xylazine to sensitise the heart to catecholamine-induced arrhythmias could also contribute to complications. A stressed animal will already have elevated catecholamine levels and the addition of xylazine and potentially halothane (also potentiating catecholamine induced arrhythmias) could result in ventricular arrhythmias and cardiac arrest. One of the cases reported by Clarke and Hall (1990) was an aggressive dog that had to be forcefully restrained prior to anaesthesia and catecholamine induced arrhythmias was a likely cause of death.

The risk associated with medetomidine, a more recent and more specific alpha$_2$ adrenoceptor agonist, is unknown, as medetomidine was introduced after the main small animal studies were published (Clarke and Hall 1990; Dodman and Lamb 1992;

Dyson, Maxie et al. 1998). Its' actions are broadly similar to those of xylazine (Cullen 1996; Pyendop and Verstegen 1998; Pyendop and Verstegen 1999). However it has not been found to sensitise the heart to catecholamine induce arrhythmias (Pettifer, Dyson et al. 1996) and this may reduce the risk associated with its use. Medetomidine is a commonly used sedative and premedicant in small animal practice (Wagner and Hellyer 2000; Nicholson and Watson 2001) and establishing its relative safety would be valuable.

Acepromazine is another common premedicant used in practice (Clarke and Hall 1990; Wagner and Hellyer 2000; Nicholson and Watson 2001) and one associated in observational studies with reduced risk (Clarke and Hall 1990; Johnston, Taylor et al. 1995; Dyson, Maxie et al. 1998; Johnston, Eastment et al. 2002; Brodbelt, Hammond et al. 2005). It causes vasodilatation and hypotension, with minimal direct cardiac or respiratory depression (Hall and Clarke 1991; Stepien, Bonagura et al. 1995). It increases the threshold to catecholamine-induced arrhythmias (Muir, Werner et al. 1975; Dyson and Pettifer 1997). Additionally, by reducing subsequently administered anaesthetic agent requirements it is can reduce cardiopulmonary depression of the patient (Heard, Webb et al. 1986; Webb and O'Brien 1988; Hall and Clarke 1991).

The risk associated with halothane, isoflurane and other inhalation agents has not been fully evaluated in the small animal literature and where studied, isoflurane has been associated with increased risk (Dyson, Maxie et al. 1998; Brodbelt, Hammond et al. 2005). This may reflect more the selection of this agent for higher risk patients than its actual safety. However it does induce more respiratory depression than halothane and if a genuine increased risk has been observed, hypoventilation could be the underlying reason (Steffey and Howland 1977; Hellebrekers 1986; Grandy, Hodgson et al. 1989; Hodgson, Dunlop et al. 1998). Isoflurane induces less myocardial depression and sensitises the heart less to catecholamine-induced arrhythmias and from a cardiovascular perspective would appear safer than halothane (Joas and Stevens 1971; Steffey, Gillespie et al. 1975; Steffey and Howland 1977; Hellebrekers 1986; Tranquilli, Thurmon et al. 1988; Grandy, Hodgson et al. 1989; Lemke, Tranquilli et al. 1993; Hikasa, Okabe et al. 1996; Hikasa, Ohe et al. 1997; Hodgson, Dunlop et al. 1998). Interestingly in young horses, isoflurane was associated with reduced odds relative to halothane (Eastment, Johnston et al. 2002).

Intubation of cats has been linked with increased risk (Clarke and Hall 1990; Dyson, Maxie et al. 1998). Cats are prone to laryngeal spasm and greater care must be taken when intubating this species than in dogs (Hall and Taylor 1994). Additionally, given their small tracheal diameters, they are more prone to obstruction with secretions, debris and blood. Premedication with an anticholinergic that reduces airway secretion may reduce this risk and interestingly Clarke and Hall (1990) found lower death rates in those premedicated with atropine.

1.4.4.4 Monitoring and personnel related risks

In small animal anaesthesia the main factor associated with increased risk was the lack of a separate person monitoring anaesthesia (Clarke and Hall 1990; Dyson, Maxie et al. 1998). This is not surprising as without careful monitoring of the anaesthetic, avoiding complications is less likely. Increased anaesthetic experience of these people has not been associated with reduced risk and in one study was associated with increased risk (Johnston, Eastment et al. 2002). The authors reflected that this was more likely to be a result of the more experienced anaesthetist undertaking higher risk anaesthesia than their increasing risk *per se*.

Monitoring equipment has not been carefully evaluated though the use of heart rate monitors was associated with increased risk of morbid complications (Dyson, Maxie et al. 1998). These monitors provide only a heart rate and no indication of pulse quality and may provide the clinician with a false sense of security. Additionally, they may have been used more frequently in high-risk patients. In horse, blood pressure monitoring was found to be protective against cardiac arrest (Eastment, Johnston et al. 2002). Arterial blood pressure measurement in the context of inhalation anaesthesia provides an indirect indicator of cardiac performance (Wagner and Brodbelt 1997) and may provide early warning of developing problems. Risk with blood pressure monitoring has not been evaluated in small animals and is presently uncommonly used in practice (Wagner and Hellyer 2000; Nicholson and Watson 2001). Pulse oximetry is another monitoring aid more recently introduced to veterinary practice and is gaining popularity (Wagner and Hellyer 2000; Nicholson and Watson 2001). It has been used in medical anaesthesia for some time and allows early recognition of haemoglobin desaturation and cyanosis (Adams 1989). Its role in anaesthetic safety in small animals

has not been evaluated.

In summary, a number of risk factors identified in the literature are supported by experimental work that provides plausible mechanisms of action of the factors. Though causation is not established, the hypothesized biological aetiologies add greater strength to the associations published in these observational studies.

1.5 Methodology

Observational and intervention studies have been used to investigate anaesthetic complications. Intervention studies have the advantage that they are less prone to problems of confounding than observational studies when randomisation of the intervention is undertaken (Hennekens and Buring 1987). However, they are more costly to undertake and may introduce ethical issues when one intervention group is exposed to an exposure factor of known increased risk. Observational studies in contrast do not generally suffer this ethical concern, though issues of bias and confounding may be more problematic (Thrusfield 1986; Hennekens and Buring 1987).

1.5.1 Observational studies

Observational studies are able to evaluate multiple factors simultaneously, are often cheaper to undertake and do not present ethical problems (Hennekens and Buring 1987). They are well suited to the study of anaesthetic complications and represent the majority of studies reported in the literature on anaesthetic complications.

1.5.1.1 Case series and reports

The early reports of anaesthetic complications took the form of case reports and series (Phillips, Frazier et al. 1960; Langley 1976; Gillick 1981; Holland 1987; Caplan, Posner et al. 1990; Gannon 1991). Though providing interesting evidence for potential risk factors, these studies did not give quantitative data and did not allow assessment of disease risks or associations with risk factors (Hennekens and Buring 1987). Hence case reports and series are most valuable as reports to base hypotheses on and to encourage the undertaking of analytical studies.

1.5.1.2 Cohort studies

The vast majority of the veterinary anaesthetic and medical complications literature has taken the form of cohort studies. Cohort studies have the advantage that they allow assessment of multiple outcomes, they allow the calculation of disease incidence risks and they are well suited to evaluating rare exposures (Schlesselman 1982; Hennekens and Buring 1987). The study of morbidity and mortality involves multiple outcomes and in theory is well suited to the cohort methodology. Prospective cohort studies, in which the studies are initiated before the outcome of interest has occurred, additionally have the advantages of a clear temporal sequence from exposure to outcome and are less susceptible to bias in the selection of participants and the ascertainment of exposure status, than case-control or retrospective cohorts (Hennekens and Buring 1987). However, in general cohort studies can be expensive and time consuming, losses to follow-up are a concern, and they are inefficient in the evaluation of rare outcomes, such as anaesthetic death (Schlesselman 1982; Hennekens and Buring 1987).

When a case-control is inserted into a cohort, forming a nested case-control, the cost of a cohort study can be considerably reduced (Hennekens and Buring 1987). The assessment of a number of risk factors in only a subset of the population at risk (i.e. the cases and controls of the study population) can be an efficient method of evaluating a problem where a diagnostic test is expensive or the outcome rare. This method is particularly suited to the evaluation of anaesthetic mortality, though only more recently has it been applied in the literature (Newland, Ellis et al. 2002; Brodbelt, Hammond et al. 2005).

In the design of a cohort study the methods of selection of the exposed and unexposed patients is an important consideration and the two groups must be as similar as possible, save for the factor under investigation (Hennekens and Buring 1987). Sources of exposure and outcome information must be carefully considered and should be as complete, comparable and as unbiased as possible. Of particular relevance to studies of anaesthetic complications is the approach to follow-up. Failure to obtain complete outcome data, i.e. losses to follow-up, is a major concern in cohort studies and in the context of anaesthetic complications setting a prolonged period of follow-up increases the proportion of lost outcome data. Additionally, a long postoperative follow-up period may increase the chance of including non-anaesthetic related complications. This

must be balanced against having too short a follow-up period and missing some anaesthetic related complications that occur after the specified postoperative period has finished. In the medical literature up to 30 days postoperatively has been studied (Lunn and Mushin 1982) whilst in equine anaesthesia a period of 7 days was recently considered (Johnston, Taylor et al. 1995; Johnston, Eastment et al. 2002). In small animal anaesthesia shorter periods have generally been evaluated and unlike in the horse, conditions such as postoperative myopathy or colic involving prolonged intensive care and subsequent death are unlikely to occur. The exception to this is postoperative renal failure, which is a serious risk in small animal anaesthesia, but is unlikely to be recorded unless the outcome is followed for a number of weeks (Hall and Taylor 1994).

Cohort studies allow the calculation of incidence rates and risks in the exposed and unexposed groups. The major comparative measure of the cohort study is relative risk. The relative risk (RR) quantifies the association between exposure and disease and represents the incidence of disease in the exposed group relative to that in the unexposed group. This can be expressed as a risk ratio when the cumulative incidence in the exposed is compared to the unexposed group or as a rate ratio when the incidence rate in the exposed is compared to that of the unexposed (Hennekens and Buring 1987).

1.5.1.3 Case-Control studies

The case-control study has the advantage over the cohort study of being an efficient method for evaluating rare diseases and diseases with long latencies, is generally inexpensive, requires relatively few subjects and allows assessment of multiple exposure factors. However, the case-control study is inefficient for evaluating rare exposures and multiple outcomes (Schlesselman 1982; Hennekens and Buring 1987). In the context of anaesthetic complications, they are an efficient method in assessing mortality, a rare outcome, but not morbidity, which involves multiple outcomes. In the medical work only a few case-control studies have been published (Campling, Devlin et al. 1990; Campling, Devlin et al. 1992; Campling, Devlin et al. 1993; Howell, Sear et al. 1998; Howell, Sear et al. 1999; Newland, Ellis et al. 2002). In the veterinary literature one small animal preliminary report has been published using the case-control method (Brodbelt, Hammond et al. 2005), and a more comprehensive equine study has been undertaken though has yet to be analysed (Johnston 2003).

The major potential problem in case-control studies is bias in the selection of cases or controls (Hennekens and Buring 1987). The exposure and outcome have often both occurred before the study is initiated and knowledge of the antecedent exposures may influence the selection of the cases or controls. Of particular concern is the selection of the controls. The controls are intended to provide an estimate of the exposure rate that would have been expected to occur in the cases if there were no association between exposure and the study disease and hence should be representative of the population from which the cases were derived (Schlesselman 1982). Insuring these controls are representative is a major problem that threatens any comparisons made between case and controls.

Hence, sampling procedures for the selection of cases and controls must aim for unbiased ascertainment of eligible cases and controls. When all eligible cases are used, as generally occurs in anaesthetic mortality studies, sampling of the controls is the main concern. Random sampling should minimise the risk of selection bias, but this often requires data on the underlying cohort (Dohoo, Martin et al. 2003). A process of control selection often seen in the medical literature is matching. Matching refers to the selection of one or more controls for each case on the basis of similarity of a factor (or factors) other than the factors under investigation (Dohoo, Martin et al. 2003). It is used to increase the power of the study and reduce bias, and often characteristics thought to be confounders of the study are chosen as matching characteristics. Disadvantages of matching include increasing the complexity of the study, precluding the evaluation of the matched factor, requiring matching in the analysis, and the possibility of overmatching reducing the validity or statistical efficiency of the study (Schlesselman 1982; Hennekens and Buring 1987).

Case-control studies also allow the quantitative assessment of the association of disease with exposures (i.e. risk factors) within a given population. The relative odds of exposure to factors of interest are compared between cases and controls giving an odds ratio (OR) of exposure. Mathematically this is equivalent to the odds ratio of disease in the cases compared to the controls (Schlesselman 1982; Hennekens and Buring 1987)

OR of exposure = odds of exposure in the cases / odds of exposure in the controls

OR of disease = odds of disease in the exposed / odds of disease in the unexposed

For rare diseases the risk of disease (where cases are included in the denominator) is similar to the odds of disease (cases are not included in the denominator) and hence the odds ratio is said to approximate the risk ratio or rate ratio. This is the rare disease assumption. More recently, it has been shown that the rare disease assumption is not required to obtain measures of the risk ratio and rate ratio if certain conditions of sampling are met (Smith, Rodrigues et al. 1984; Rodrigues and Kirkwood 1990).

In conclusion, the cohort and case control methodologies are both suited to the investigation of anaesthetic complications. Cohorts are particularly appropriate to morbidity studies with common outcomes and for studies with multiple outcomes. Case-control studies allow assessment of the rare disease of anaesthetic mortality and are cheaper to perform. In the context of anaesthetic mortality the nested case control is particularly useful as anaesthetic death risks and risk factors may be assessed efficiently.

1.5.2 Intervention studies

Intervention studies provide the strongest epidemiological evidence for causation but may be unfeasible when multiple factors are to be assessed. Their key feature of randomisation of the allocation of patients to study groups reduces bias and controls for both known and unknown confounding variables (Sackett, Straus et al. 2000). Intervention studies however, may be prohibitively expensive and may be unethical if a study group is exposed to known harmful factors or deprived of known beneficial factors (Hennekens and Buring 1987). Only a few clinical trials have been published in the anaesthetic complications literature and have focused on specific aspects such as the risk with different inhalation agents (Forrest, Cahalan et al. 1990; Forrest, Rehder et al. 1992; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004). In the medical literature the work of Forrest and colleagues (1990; 1992) evaluated four anaesthetic regimes. It compared risks of morbid complications between experimental groups but had insufficient power to compare risk of death between groups. In the veterinary literature only one study has been published and evaluated the risk of death when using halothane and isoflurane in horses (Eastment, Johnston et al. 2002; Johnston, Eastment

et al. 2004). It did not find an overall significant difference between isoflurane and halothane, though found a reduced risk when using isoflurane in young horses.

Hence though valuable in evaluating the relative safety of different anaesthetics, intervention studies are often too specific in their focus to be applied when evaluating anaesthetic complications. They are best used after observational studies have thoroughly investigated anaesthetic risks, when specific hypotheses need further testing to establish causation.

Chapter 2: Materials and Methods

2.1 Introduction

The study anaesthetic-related death is a rare outcome and as such could be efficiently evaluated with the case-control study method (Schlesselman 1982; Hennekens and Buring 1987). Nesting the case-control study within the cohort of all anaesthetised small animals at participating centres allowed the estimation of the risk of anaesthetic-related death in these species. A prospective multi-centre study, based on this methodology, was undertaken in the UK to evaluate anaesthetic-related death in small animal practice.

2.2 Pilot Study

A pilot study was undertaken between 1st of June and the 1st of October 2002 to refine *a priori* hypotheses and to identify additional study hypotheses, to test and modify the study method and data collection tools, and to revise the power and sample size calculations for the main study. Practices were requested to take part in the study as described below, and interested centres were contacted by the primary investigator. After discussing the nature of the study, the time period anticipated for the study and the likely workload for individual centres, interested centres were recruited and a practice file, including all questionnaires was delivered to them. Fifty-three centres were recruited on an ongoing basis during the pilot study during the first two-months of the four-month pilot. Most centres were visited during the pilot study.

At the end of the pilot study, species-specific mortality risks were estimated and crude odds ratios were calculated for a number of risk factors identified by *a priori* hypotheses and by previous studies. The results were then used to adjust *a priori* hypotheses, to reassess sample size calculations, and to modify the method for the main study. Preliminary results were distributed to participating centres and they were encouraged to continue with the study. Additional centres, primarily larger centres, were then recruited to the main study.

2.3 Power calculations and sample size estimates

Prior to the pilot study, the study was designed to have a 90% power to detect associations of factors with odds ratios of at least 2.5 and present in 5% of controls. Using an efficient 1:4 case control ratio (Schlesselman 1982), around 230 cases and 920 controls would be required in dogs and cats. Assuming a mortality risk, based on previous work of 0.1% (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000), and a case notification rate of 95%, approximately 265,000 anaesthetics would need to be recorded in both species. It was estimated that this number of anaesthetic events and cases could be recorded over a two-year study period, if 70 large clinics that performed an average of 7 anaesthetics and sedations a day in both cats and dogs were recruited, assuming a 260 day working year.

In light of the pilot study, this sample size calculation was revised based on a revised primary hypothesis. From the pilot study it was calculated that patients' receiving medetomidine compared to not receiving medetomidine were approximately at a two to three-fold reduction in risk of death. Assuming the presence of this factor in dogs in a least 13% of the population, based on an odds ratio of 0.3 at a power of 90% and confidence level of 95%, then approximately 140 cases and 560 controls (case: control ratio 1:4) would be required in dogs. In cats assuming, a level of exposure of 25% and an odds ratio of 0.5, then 180 cases and 720 controls would be required at the same power and confidence level. The risk of mortality based on the pilot study was higher than expected and based on the revised risk, approximately 60,000 to 90,000 anaesthetic events would be required in dogs and cats. This could be achieved within the study period by recruiting a number of additional clinics, generating a total of approximately 5,000 anaesthetics a month in dogs and cats. These revised targets would still provide sufficient power to address a number of other risk factors with similar or more common exposure frequencies in the control population to those reported for the stated hypothesis, assuming similarly biologically significant odds ratios.

2.4 Aims and Objectives

The aims of the study were to evaluate anaesthetic-related death in small animal practice and to provide information to help reduce mortality. The objectives of the study

were to:

a. Describe trends in the practice of small animal anaesthesia.

b. Estimate the risk of anaesthetic and sedation-related mortality in dogs, cats and 'exotic' species

c. Describe the causes of anaesthetic-related death

d. Identify risk factors for anaesthetic-related death in dogs, cats and rabbits

e. Identify risk factors for anaesthetic-related death in 'sick' (ASA grade 3-5) dogs and cats

f. Make recommendations to improve the practice of small animal anaesthesia

2.5 A Priori Hypotheses

Hypotheses, pertaining to the dog and cat populations and anaesthetic-related death, were prepared prior to the start of the study based on previous published work and clinical experiences and modified where appropriate in light of the pilot study. They included the following hypotheses:

a. Sick patients (ASA grade 3-5, Appendix 2.1) are at an increased risk of death compared to healthy (ASA 1-2) patients.

b. The use of acepromazine is associated with a two-fold reduction in the odds of death.

c. The use of medetomidine is associated with a two-fold reduction in odds of death.

d. Induction of anaesthesia with propofol is associated with a two-fold reduction in odds of death compared to thiopentone.

e. Maintenance of anaesthesia with isoflurane is associated with a two-fold reduction in odds of death compared to halothane.

f. The use of intraoperative fluids is associated with a two-fold reduction in odds of death.

g. Endotracheal intubation in cats is associated with increased odds.

h. Having a separate person monitoring anaesthesia is associated with a two-fold reduction in the odds of anaesthetic-related death.

The initial hypothesis in relation to medetomidine was that it was associated with a two-fold increase in odds of anaesthetic related death. In light of the pilot study results this was modified to a two-fold reduction in odds.

2.6 Study population

The study population consisted of all small animals anaesthetised or sedated by the participating clinics during their period of participation. Anaesthesia was defined as chemical restraint, sufficient to allow endotracheal intubation (independent of whether endotracheal intubation was performed). Sedation was defined as chemical restraint insufficient to allow endotracheal intubation. For the purpose of this report 'anaesthesia' will include anaesthesia and sedation unless stated otherwise. The need for good compliance and high quality data over an extended study period suggested that recruiting interested and motivated centres was a greater priority than involving clinics that more closely represented the distribution of UK practices. For this reason a convenience sample of veterinary practices and referral veterinary institutions in the UK were recruited to participate in the study.

2.7 Study design

A nested case-control design was used to investigate the aims and objectives and to test the hypotheses of the study. A nested case-control study is a case-control study that draws its cases and controls from a pre-determined cohort population that has been followed for a period of time (Dohoo, Martin et al. 2003). The cohort study recorded all anaesthetics and sedations undertaken and all deaths within 48 hours of anesthesia, allowing the estimation of the risks or death. The case-control study was undertaken within the framework of the cohort. The cohort provided a source population from

which to identify the controls and the anaesthetic-related deaths. The case-control study was performed to identify risk factors associated with anaesthetic-related death.

2.7.1 Cohort study

All anaesthetic and sedation events occurring at participating centre were recorded and the risks of perioperative mortality within 48 hours after the procedure were estimated. The cohort data were recorded as self-administered questionnaires by the centres and returned on a monthly basis in prepaid envelopes. The questionnaires and envelopes were supplied at the beginning of the study to participating centres in a CEPSAF study file with information on the study. Additional forms were sent to the centres throughout the study period as completed questionnaires were returned to ensure all centres always had surplus questionnaires and envelopes.

Information was recorded in case diary forms (Appendix 2.2) supplied to the clinics and included the unique centre code, procedure date, patient identification, species, whether it received an anaesthetic or sedation, and outcome at 48 hours (recorded as alive, dead or euthanased). Brief details of the reason for death or euthanasia were recorded in the diary for patients that died. The method of identification of patient outcome was left to the individual centres and focused on that method by which the practice was confident they would be able to record the correct outcome. Methods included active communication with the owners via a 48-hour postoperative practice consultation or telephone check-up, and passive responses by the patients' owners to the practice if a postoperative fatality occurred. Losses to follow-up were checked with the practices and the outcome ascertained when possible. Fifteen cats and twenty dogs were recorded in the cohort with an unknown outcome during the study period (0.02%) and these patients were excluded from the denominator of patients anaesthetised during the study.

Risks of mortality and euthanasia were estimated and species-specific risks of anaesthetic-related death were calculated from the number of anaesthetic-related deaths divided by the number of patients anaesthetised or sedated in the cohort.

2.7.2 Case-control study

The case-control study investigated risk factors for anaesthetic-related death. Information on the covariates of interest was recorded on the same questionnaire for

cases and controls and included patient and procedure details, anaesthetic and postoperative management, and personnel-related variables (Appendix 2.3). Descriptive information on the timing of death, clinical signs and circumstances of death, post-mortem results, cause of death and role of anaesthesia were recorded for the cases. The questionnaires were self-administered by the centres and were returned in postage paid envelopes after completion. Questionnaires were supplied to the centres at the start and throughout the study in the CEPSAF study file with the cohort questionnaires. Additional forms were sent to the centres throughout the study period as completed questionnaires were returned to ensure all centres always had surplus questionnaires. The selection method of the controls is described below.

2.7.2.1 Species specific studies

Separate case-control studies were undertaken for dogs, cats, rabbits, sick dogs and sick cats. The case-control studies in the dogs, cats and rabbits were nested in the species-specific cohorts described above. Risk factors were evaluated separately in these three species. Separate case-control studies were undertaken in a subpopulation of 'sick' (ASA grade 3-5, Appendix 2.1) dogs and cats.

2.7.2.2 Case definition and selection

A case was defined as a perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death or euthanasia was due solely to inoperable surgical or pre-existing medical conditions. A death was considered a case if anaesthesia could not be reasonably excluded as a contributory factor. Cases were identified by the participating centres in the first instance and subsequently by the investigators from the cohort of anaesthetics recorded by each practice. Deaths recorded in the cohort, but for which no case-control questionnaire was submitted by the clinic, were investigated and a case-control questionnaire was requested if the death could be considered a case. Case-control questionnaires were requested for all potential cases in all small animal species (dogs, cats and exotics) to allow for estimation of risks of anaesthetic-related death. In dogs, 15 out of 285 deaths were unaccounted for (case notification rate of 95%), whilst in cats, 14 out of 248 deaths were unaccounted for (94%).

The classification of dog and cat cases was undertaken by an independent review panel. All potential cases were assessed based on the case definition and a set of documented criteria **(**Appendix 2.4). The criteria formalised the decision process for classifying fatalities as cases, and assessed the body of evidence for anaesthesia contributing to the death for each case in light of the timing of the death and proximity to the completion of the anaesthetic (if a postoperative death), the patient's pre-existing health status, and the likely contribution of the procedure to the death. The panel consisted of two RCVS diploma level veterinary anaesthetists, an RCVS diploma level veterinary soft tissue surgeon and was chaired by an experienced veterinary scientist with a RCVS Diploma in Veterinary Anaesthesia. The panel met for two sessions over three days during the study. The panel was unaware of the clinics' identity and the drugs administered. The panel also classified the primary cause of death, based on a list of possible causes (Appendix 2.5). The panel's decision was accepted as final for all classifications.

Cases were excluded from the analysis if they occurred prior to the administration of an anaesthetic agents (including premedication) or if they occurred beyond 48 hours after termination of anaesthesia. Fatalities that did not satisfy the case definition were excluded. Cases in which insufficient information was available were also excluded from the analysis (15 dogs and 14 cats for which no questionnaire was returned and for which there was insufficient information to exclude them from being cases).

For the rabbit dataset, only cases occurring between the 1st of January 2003 and the 31st December 2003 and that had returned a matched control, were included in the analysis of risk factors. Rabbit cases outside this time period and for which no matched control were received were excluded from the analyses of risk factors. These cases were included in the numerator number of cases when species-specific anaesthetic-related risks of mortality were estimated.

Case selection followed the same procedure as in the dogs and cats, though the primary investigator classified the cases in rabbits (and the anaesthetic-related deaths in all other 'exotic' animal species), and the primary cause of death based on the criteria described above.

2.7.2.3 Control definition and selection

Controls were defined as dogs or cats that had been anaesthetised, that did not die (or were not euthanased) within 48 hours of termination of the procedure, and that were derived from the cohort of dog and cat anaesthetics. Dog and cat controls were prospectively randomly selected from the cohort of dogs and cats anaesthetised at a 1:4 case to control ratio. This was designed to be an efficient ratio, given the number of anticipated cases and the estimated investigator and clinic workload in gaining this control information (Schlesselman 1982). A patient could serve as a control for more than one anaesthetic event. That is, an animal could be randomly selected as a control for two or more anaesthetics if it was anaesthetised on more than one occasion. The same patient could not be selected more than once as a control for the same anaesthetic episode. A case could serve as a control for all prior anaesthetic episodes.

The randomly selected controls were identified from the cohort data. The monthly clinic species-specific anaesthetic and sedation totals were entered into a relational database (Access, Microsoft), exported to a spreadsheet (Excel, Microsoft) and cumulative frequencies of anaesthetic events were calculated by clinic for dogs and cats. This allowed the identification of individual dog and cat anaesthetic events by clinic number and within that clinic the patient number of the month. Thus a patient would be randomly selected from the monthly cohort and then identified by clinic and the specific patient number of the month for that clinic (e.g. 53rd dog of 112 dog anaesthetics that month in clinic 1115). The previous month's distribution of anaesthetic events was used to generate the following month's controls. The controls were identified by clinic number, species, procedure number of the day, day of the week and week of the month based on the previous month's distribution. For example, the 53rd dog would have been the 3rd dog anaesthetised on the 2nd Tuesday of the month at clinic 1115, based on clinic 1115's previous month's cohort data. The 3rd dog anaesthetised on the 2nd Tuesday of the current month at clinic 1115, would then be requested shortly after the 2nd Tuesday.

The number of controls prospectively randomly selected each month was based on the number of cases that occurred in the previous month, multiplied by the number of controls required per case. Initially, over the first 6 months of the main study, the number of cases occurred faster than anticipated and the number of controls requested was lower than the global target of 4 per case (approximately 2-3 controls requested

per case during this early period). As the study progressed the monthly numbers of controls was readjusted to reach the anticipated global targets (Appendix 2.6).

The clinics were contacted by phone, email or post by the primary investigator, soon after the specified control was anaesthetised and completion of the case-control questionnaire was requested retrospectively to allow retrospective completion of the form as for the cases. If the same random number was drawn more than once, the random selection process was repeated for all but the first selection of that control. Control questionnaires that were not received from the clinic within 2 months of request, were reallocated to the same clinic for the next month (i.e. the 3rd month after request). The patient of the same species, operation number, day and week of the month as for the original selection, was requested from this subsequent month.

In the study of sick animals, Sick controls were defined as high-risk status patients (ASA grade 3-5, Appendix 2.1) that did not die within 48 hours of anaesthesia. Sick patients ranged from animals with severe disease limiting activity but not incapacitating, to patients moribund and not expected to live. The overall study controls randomly selected from the cohort as described above, were included as Sick controls if they were classified as sick (i.e. ASA grade 3-5). Additional sick controls were prospectively randomly selected from the cohort of sick dogs and cats anaesthetised during the study period to make up an overall 1:1 case to control ratio. The randomisation process for the additional Sick controls was undertaken in a similar manner as described above, with the clinic number, day and operation of the day identified. The distribution of the sick caseload was assumed to be similar to the overall study caseload across the clinics in the randomisation process. Practices were then contacted and the specified Sick patient was requested for a given date prior to the request date. The Sick controls could serve as a control for more than one anaesthetic episode, but could not serve as a further control for the same episode. A case could serve as a Sick control for all prior anaesthetic episodes.

Rabbit controls were matched to the case by clinic and proximity of time to the case, at a 1:1 case to control ratio. The most recent rabbit non-fatality anaesthetised at the same centre prior to the case was elected as the control unless it was anaesthetised more than two months before the case. If the latter, the most recent rabbit after the case was chosen. Cases could serve as controls for anaesthetic episodes prior to the episode

that ended in death (as long as the patient died at least 48 hours after the anaesthetic selected as a control) and rabbits could be selected more than once as a control for separate anaesthetic episodes.

Controls were excluded from the analysis if they died or were euthanased within 48 hours of termination of the procedure. Sick controls were additionally excluded if they were classified preoperatively by the centre as risk-status ASA 1 to 2 but still submitted as sick controls by the centre or if they were classified by the centre as ASA 3-5 but subsequently reclassified as ASA 1-2 by the author after discussion with the centre. Cases and controls were excluded from the analysis if a substantial percentage of data were not recorded (e.g. drugs used uncertain and recovery times not known)**.** Data from the one centre outside the UK were excluded from the analysis. Data recorded during the pilot study were included in the overall statistical analysis.

2.7.3 Survey of Practice Characteristics

A questionnaire of practice characteristics was completed by all centres. This questionnaire (Appendix 2.7) evaluated the characteristics of the practice, the number of vets and nurses undertaking small animal work, the anticipated weekly workload, the experience of the personnel and their routine anaesthetic management of small animals. It also investigated the centres' perceptions of their risk of anaesthetic-related mortality and allowed cross-checking of data recorded in the case-control questionnaire. This survey was undertaken as face-to-face interviews by the primary investigator at the participating centre, except where geographical or time considerations made it difficult to attend the centre. In these latter cases the form was posted to the centres and was self-administered. Of 118 centres that participated, 1 was excluded (see results), 73 were visited (62% of non-excluded centres) and 44 were not visited (38%).

2.8 Recruitment, Training and Retention of Centres

Interested practices and referral centres were invited to join the study. The study was publicised by publishing letters and short articles in the veterinary press, explaining the nature of the study, the likely workload for individual clinics, the benefits to the participating centres and requesting volunteers to take part. Oral presentations were

undertaken at a number of veterinary meetings around the country to encourage recruitment. Additionally, after the pilot study, all 72 registered veterinary hospitals recorded on an electronic database (Royal College of Veterinary Surgeons Practice Directory, electronic version), were written to, requesting further volunteers, followed by a telephone call to discuss potential participation, and 49 took part in the study (68%). The study sought and received scientific endorsement from the Association of Veterinary Anaesthetists, the British Small Animal Veterinary Association and the British Veterinary Hospital Association. The endorsements raised the profile of the study and aided recruitment of clinics.

Recruited centres were sent a practice file including all data-collection tools. All clinics were identified by a unique four-digit code only and anonymity of data was assured. The primary investigator visited or rang all centres soon after delivery of the file to explain the study method, answer queries and establish primary and secondary contacts within the centre. A follow-up call was undertaken approximately one month later to check progress and answer further questions. Thereafter, ongoing training and contact with the centres was regularly maintained with communication by telephone, post, email and fax. All returned data were individually acknowledged and specific queries were addressed and errors or omissions in the returned data were discussed with the centres. Most centres were visited during the study, except for those centres where geographical distance made a visit difficult (73 of 118 centres were visited, 62%). At these visits further training and data validation were undertaken by discussing further questions the centres had with the study, checking data queries and by comparing the study's recorded caseload with that recorded in the practices operations book or other records when available. The survey of the practice facilities, personnel and anaesthetic drugs used was undertaken at these visits.

Regular feedback of information in the form of study updates was undertaken on a six-monthly basis to aid retention of centres. Biscuits were sent out with these updates to acknowledge the centres commitment to the study, maintain enthusiasm for the study and the quality of the data recorded.

2.9 Data collection tool design

Data were recorded on paper-based questionnaires. These questionnaires were pre-tested on four veterinary surgeons and one nurses in practice and at veterinary institutions prior to the study. Veterinary epidemiologists Kristien Verheyen, James Wood at the Animal Health Trust and Dirk Pfeiffer at the Royal Veterinary College also evaluated them at this time. They were then tested in the pilot study and minor modifications were made prior to continuing with the main study (Schlesselman 1982). The final questionnaires were then professionally formatted and printed on yellow paper to aid data collection (Salant and Dillman 1994; Dohoo, Martin et al. 2003)(Appendices 2.2 and 2.3).

2.9.1 Cohort Study Diary.

The Diary format ('CEPSAF Diary') was designed to record efficiently the required information. Data for individual animals were recorded on one-line entries. The unique four-digit clinic code was recorded by the primary investigator in the top right of each diary page prior to delivery to the clinic, and a page number box was placed at the top of each page to allow centres to record the sheet number. Instructions directing clinics to complete the one-line entry for all anaesthetics and sedations undertaken at the centre in all small animal species during the study period were printed at the top of each page. Instructions relating to each field of the diary sheet, including the case definition, were printed on the reverse of the form. The address and facsimile number, to which the forms were to be returned to, were included on each sheet.

Following the findings in the pilot study, a case-control questionnaire was requested for all potential cases in other small animal species (i.e. 'exotics'), if they satisfied the case definition. A short description of the reason for death or euthanasia was also requested for each anaesthetic or sedation that died (or was euthanased within 48 hours), to aid the investigators' verification that case-control questionnaires had been completed for all possible cases. An additional box was added to the form at this stage to allow practices operating at more than one centre to indicate which branch was submitting the diary forms. This allowed the identification of the branch when randomising controls. A small number of centres completed the dairy in an electronic format, after an initial period of

completing both the paper and electronic version. The parallel recording of both paper and electronic versions allowed comparison to the electronic format.

2.9.2 Case-Control Study

Instructions pertaining to the completion of the form and the definition of a case were printed on the front page. The unique clinic number was recorded by the primary investigator prior to delivery to the centre on the front page and remained the only method of identifying the centre returning the form. The importance of anonymity of the data returned was emphasised.

The case-control questionnaire was designed to record detailed information relating to all aspects of the selected anaesthetic or sedation. Questions were grouped logically in sections relating to the patient's characteristics and preoperative evaluation, the procedure intended, the anaesthetic management (including postoperative care) and monitoring of the patient, information on the personnel involved in the procedure, and for deaths the details of the timing and nature of the fatality. Questions generally took a closed format with only specified responses permitted. This allowed efficient coding and categorization of responses (Schlesselman 1982; Dohoo, Martin et al. 2003). Open-ended questions were reserved for continuous data (e.g. weight or age) and where further explanatory comments were invited. The latter had the advantage of allowing a greater depth of information being recorded (Dohoo, Martin et al. 2003) and were primarily used to clarify or corroborate issues (e.g. if anaesthetic related or not, patient health status). A semi-open format was applied in some questions to allow uncommon responses to be recorded and to invite respondents to volunteer further information (Dohoo, Martin et al. 2003).

Subsequent to the pilot study some questions were modified or removed and additionally a few questions were added. The format of the questionnaire was reduced from 12 A4 pages to 8 A4 pages and was bound as two double-sided A3 pages. The questionnaire was again professionally formatted after the pilot study and printed on yellow paper.

2.9.3 Practice Survey Questionnaire

The practice survey was designed as a three-page questionnaire. Primarily, closed and semi-open questions were used. This questionnaire was modified in light of the pilot study and additional questions were added relating to drugs commonly used.

2.10 Database design

A dedicated relational database was designed (Access 2000, Microsoft). Separate tables were constructed for each of the three questionnaires (case diary, case-control and practice survey). Details of the practice address and primary and secondary contacts at the centre were recorded in a separate table. The tables were linked by the clinic identification code. An additional table was constructed for the outcome data for less common exotic species (i.e. not including rabbits, guinea pigs, hamsters or ferrets). For the case diary data, a record consisted of the individual clinic's monthly species-specific numbers of anaesthetics and sedations undertaken, and the corresponding number of euthanasias and deaths occurring during the month for dogs, cats, rabbits, guinea pigs, hamsters and ferrets. For all other exotic species the same information was recorded as species monthly totals. For the case-control questionnaires a record consisted of all data pertaining to a specific anaesthetic event and was given a unique form number in addition to the clinic number. Due to the number of explanatory variables in the case-control dataset, the data were recorded in two linked tables. The two tables were linked by the practice's identification number and the individual form number. For the practice survey, a record consisted of all information recorded in the practice survey and was identified by the unique practice identification number only.

Database forms were designed for each table and mirrored the appearance of the respective questionnaires, except for the case diary information in which only the species-specific monthly totals were recorded. For the practice survey and case-control questionnaires all question numbers on the database forms corresponded to the respective form numbers on the questionnaires. Categorical data were displayed as the descriptive category labels bound to the numerical code. The bound numerical codes were recorded as the data.

2.11 Data validation, checking and cleaning

Upon receipt, all data were checked for inconsistencies, errors and omissions and the centres were contacted to clarify the data. All data were individually acknowledged by post and then were entered into the dedicated relational database. Control questionnaires were entered by students at the Royal Veterinary College and the primary investigator. These data were checked by the primary investigator, against the respective questionnaires and corrections were made when necessary. Financial and time restrictions precluded double entry. A random sample of approximately 20% of entered case-control questionnaires were checked against the questionnaires and for the cat data, 6 individual errors from 170 forms checked were noted (3.5% of forms had one error of approximately 150 data fields per form), whilst checks of 100 dog case-control questionnaires, indicated 5 errors (5%). Validation of data was carried out where possible by comparing the consistency of related explanatory variables. All cases were cross-checked to the cohort data, and when deaths were recorded in the cohort but no case-control questionnaire was submitted, the centre was contacted and a case-control questionnaire was requested if the death satisfied the case definition. Data omissions in the cohort that could not be corrected were recorded in the database in a separate field of the respective monthly clinic record.

Response bias was assessed by recording the non-response rates in cases and controls. Non-response for case-control questionnaires was evaluated by randomly checking 20% of the non-returned controls in dogs and cats, against the centre's records of those patients with regard to patient health status, age, procedure complexity (major versus minor) and urgency. These data were compared to the control population's exposure histories, to assess the differences between responding and non-responding control patients. The Student's t test was used for continuous data and 95% confidence intervals for the difference in the means were reported (Kirkwood 1988). For categorical data, the respective proportions were compared with the significance test for two proportions and confidence intervals for the difference between the proportions were calculated via the Hauck-Anderson corrected classical procedure for equivalence testing (Kirkwood 1988; Tu 1997; Christley and Reid 2003).

Comparisons of participating centres to UK practices as a whole were made by comparing a number of key indicators provided by the RCVS man-power surveys,

with data recorded in this study. This allowed comparisons to be made as to the comparability of participating practices to UK practices as a whole.

2.12 Statistical Methods

The risk of anaesthetic-related death for each species was calculated by dividing the number of cases by the total number of anaesthetic and sedation events recorded in the cohort. The risk was expressed as the percent risk, and the 95% confidence intervals (CI) were estimated as described by Kirkwood (1988).

$95\% \text{ CI} = p \pm (z)(\text{S.E.})$

$\text{S.E.} = \sqrt{(p(1-p)/n)}$

where the standard error was abbreviated by S.E., p the mortality risk, n the sample size, and z' the appropriate percentage point of the standard normal distribution ($z' \approx 1.96$ for the 95% CI). When the conditions that np and n(1-p) were greater than or equal to 10 were not met, exact confidence intervals were calculated (Kirkwood 1988).

The risk of anaesthetic-related death reported for each health status strata was estimated as it was not possible to calculate it from the data (health status was not recorded in the cohort). The denominator number of anaesthetic events for 'Healthy' and 'Sick' patients were estimated by multiplying the proportion of randomly selected controls with the respective health status (from the case-control study), by the total denominator number of anaesthetic and sedation events. The numerator numbers of healthy and sick cases were then divided by these respective denominator estimates of healthy and sick anaesthetic events to give health status specific risks.

All statistical calculations were performed with STATA software (Intercooled Stata version 7.0, Statacorp). Descriptive statistics were reported for practice, patient, procedure, personnel, and anaesthetic management characteristics. The characteristics of the population at risk were reported based on the randomly selected dog and cat case-control data and the data provided from the practice surveys. These data were expressed as the proportion of controls or clinics with the explanatory factor respectively and their 95% confidence intervals were calculated, as above. Additionally, descriptive data in

the cases, relating to the circumstances and characteristics of death, were recorded and their 95% confidence intervals were calculated as described above. The randomly selected dog and cat controls were compared to the cohort by their proportion of anaesthetics versus sedations. This provided an indication of the controls' representitiveness of the population from which they were selected. The respective proportions were compared with the significance test for two proportions and confidence intervals for the difference between the proportions were calculated via the Hauck-Anderson corrected classical procedure for equivalence testing (Kirkwood 1988; Tu 1997; Christley and Reid 2003).

Univariable analysis, to determine the association of each variable with the odds of anaesthetic-related death, was undertaken and crude odds ratios (OR) and 95% confidence intervals (CI) were calculated (Schlesselman 1982). The odds of an event represents the number of events divided by the number of non-events, such that the numerator is not included in the denominator (Dohoo, Martin et al. 2003). For example the odds of disease would be the number with the disease divided by the number without the disease. The odds ratio (OR) of disease is the odds of disease in the exposed group divided by the odds of disease in the unexposed group. Alternatively, the odds of exposure can be measured and it represents the odds of being exposed to a factor in the diseased group divided by the odds of exposure in the non-diseased group. Mathematically these are equal, though in a case-control study only the latter is generally measurable (Schlesselman 1982). An OR =1 indicates the odds are the same in the exposed and the unexposed groups (or diseased and non-diseased groups), an OR > 1 suggests the odds are greater in the exposed group and an OR < 1 indicates the odds are lower in the exposed group.

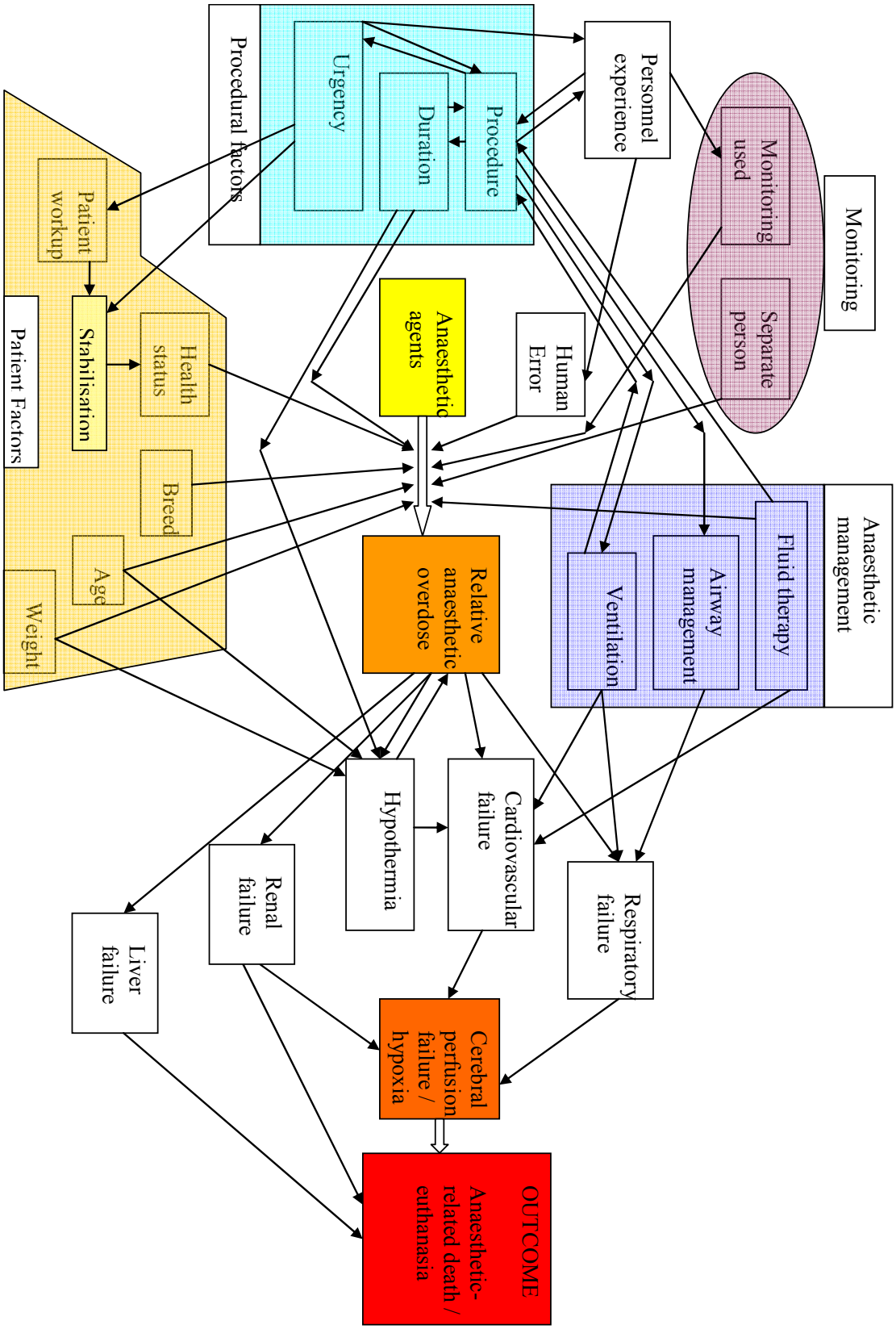
For categorical variables, the chi-squared test was applied for an approximate test of the null hypothesis of no association and the 95% confidence intervals were calculated using the standard errors obtained from the square root of the variance of the score statistic (Schlesselman 1982; Hosmer and Lemeshow 2000). When the total in the respective 2 x 2 table was less than 20 or when it was between 20 and 40 and the smallest of the expected values was less than 5, Fisher's exact test was applied and exact 95% confidence intervals were reported (Schlesselman 1982; Kirkwood 1988). If the total number were greater than 40 the chi-squared test was applied regardless of

the smallest expected value (Kirkwood 1988). Additionally, for larger tables (multiple category variables), the likelihood ratio test P value was calculated for the variable, comparing the model with the variable included to that with only the dependent outcome variable (Hosmer and Lemeshow 2000). When appropriate for multiple category variables, the odds ratio for a one category increase in odds was calculated (a one degree of freedom test for trend, 'trend') (Hosmer and Lemeshow 2000).

For the comparison of two means (i.e. between cases and controls) for continuous data, the t test was used if the data followed a normal distribution and the non-parametric Mann Whitney U test was used for non-normal data (Kirkwood 1988). Continuous variables were additionally categorised into quintiles and these quintiles were collapsed and odds ratios calculated, when exploring the data in the univariable analysis.

Exploratory stratification and Mantel-Haenszel adjusted odds ratios were calculated for preliminary evaluation of confounding and interactions (Breslow and Day 1980). Risk factors significant at the 20% level, and biologically plausible variables, were taken forward for further evaluation in the multivariable analysis. A multivariable logistic regression model was then built and the contribution of explanatory variables to the model was assessed in a manual forward stepwise selection technique (Hosmer and Lemeshow 2000). The model construction was undertaken in light of a conceptual framework constructed *a priori* (Figure 2.1). Variables were retained in the model if the variable significantly reduced residual deviance, and improved model fit as assessed by the likelihood ratio test (LRT $P < 0.05$).

Figure 2.1 Conceptual Framework for Risk Factors for Anaesthetic-Related Death



The multiple logistic regression model was given by the following equations as described by Hosmer and Lemeshow (2000), where g(x) represents the logit of the multiple logistic regression model, $\pi(x)$ the corresponding logistic regression model, $x_1 - x_p$ represent the independent variables, and β_0 to β_p the coefficients:

$$g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p$$

$$\pi(x) = e^{g(x)} / 1 + e^{g(x)}$$

Clinic was included as a random effect and a final mixed effects logistic regression model of risk factors for anaesthetic-related death was built as described by the below equation, where the random effects follow a normal distribution with mean zero and constant variance ($\alpha_i \sim N(0, \sigma_\alpha^2)$) (Hosmer and Lemeshow 2000). The statistical significance level was set at 5%.

$$g(x_{ij}, \alpha_i, \beta_s) = \alpha_i + x'_{ij}\beta_s$$

The quality of the model fit was assessed using the Hosmer-Lemeshow test statistic and by evaluating model residuals with the delta beta and delta deviance influence diagnostic statistics based on the observed covariate patterns (Hosmer and Lemeshow 2000).

For the rabbit dataset a matched analysis was performed. The maximum likelihood estimates of the odds ratios, conditional on the number of discordant pairs, were calculated for the risk factors (Schlesselman 1982). McNemar's chi-squared test was applied to test the association and 95% confidence intervals were calculated (Kirkwood 1988). A multivariable conditional logistic regression model was built (Breslow and Day 1980). Model fit was assessed by breaking the matching and evaluating the unconditional model fit as described above (Dohoo, Martin et al. 2003).

2.13 Discussion

The use of a nested case-control study approach was an efficient method for evaluating a rare disease, such as anaesthetic death, whilst allowing the estimation of incidence risk (Hennekens and Buring 1987). However, there were some limitations to this approach.

2.13.1 Cohort Study

The underlying prospective cohort allowed estimation of the risk of anaesthetic-related death. This was an efficient approach for a rare disease, however the critical issue for the cohort remained insuring complete as possible, comparable and unbiased assessment of outcome of all patients (Hennekens and Buring 1987). Classification of sedation versus anaesthesia was appropriate to veterinary anaesthesia but contrasts to human definitions in which sedation represents the retained ability of verbal response, this should be acknowledged when comparing to human work. The losses to follow-up were minimised in the design by reducing the follow-up period to 48 hours after anaesthesia, a period of follow-up likely to be identified for all patients by participating centres. Longer periods such as 7 days, as used in the equine prospective study (Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004), were considered likely to increase losses to follow-up (Hennekens and Buring 1987). This concern was considered more important that the loss of a small number of anaesthetic-related deaths occurring after 48 hours. Consequently, risk factors identified in the case-control study represented factors associated with anaesthetic-related death that occurred within 48 hours of anaesthesia. The losses to follow-up in the study were reduced by ensuring enthusiasm in participants throughout the study with constant contact, regular updates and biscuits.

2.13.2 Case-Control Study

Case definition and selection were important considerations in evaluating the limitations of this study (Hennekens and Buring 1987). The use of a simple and clear case definition and the appointment of an independent review panel to classify all dog and cat cases against a set criteria, were undertaken to increase consistency of case classification (Appendix 2.4). The controls were intended to represent the population of individuals that would have been identified and classified as cases had they developed the outcome (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Given the

population from which the cases were derived was known (i.e. the cohort), random selection of the controls across the cohort should have provided representative controls. Matched controls for the rabbit case-control study may have been less representative of the underlying population of rabbits at risk, but were undertaken to increase efficiency of administration.

Selection bias is a major concern for case-control studies (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Random selection of the controls across the cohort of anaesthetised patients should have minimised the differential selection of controls based on their exposure histories (Breslow and Day 1980; Dohoo, Martin et al. 2003). The minor tendency to controls being collected later in the study compared to cases (Appendix 2.6) could have biased the results, particularly if anaesthetic patient management changed across the practices over the study period. However, given the relatively short study time (2 years) and the fact that this was only a minor tendency, would suggest the likely degree of bias was small. The matching process of rabbit control selection was also unlikely to encourage selection bias as the exposure histories would not have influenced selection other than for the matching variables, and individual centres could not influence patient selection. Issues of non-response were an important consideration, and efforts to ensure a high response rate for cases and controls were undertaken. The recording of the return of the forms, checking with centres if case-control forms were not returned when requested, and re-randomising these forms to the same clinic later in the study period if they were still not returned were all undertaken to increase the response rate. The response rate in the cases was good at approximately 95% in both dogs and cats, whilst the 80% response rate in the dog and cat controls and the rabbit cases and controls was lower but still reasonably good (Dohoo, Martin et al. 2003). The checks on the non-returned controls were undertaken to compare the non-responders to the returned controls (Dohoo, Martin et al. 2003) and the patients appeared similar based on the variables recorded. The use of the equivalence testing approach with confidence intervals stated for the differences in proportions, in addition to significance testing, allowed clearer assessment of the differences between the non-returned and the returned controls, particularly where no differences were observed (Tu 1997; Christley and Reid 2003).

Information or observation bias, particularly errors of misclassification, was a further potential concern (Breslow and Day 1980; Dohoo, Martin et al. 2003). Misclassification of exposure histories by the clinics was minimised by data checking the case-control questionnaires against anaesthetic record forms when available, and by assessing the plausibility of the data. Data entry errors were minimised by checking the data twice and randomly checking 20% of the entered data again. In these random checks less than 5% of the cases and controls had an error. Misclassification of the outcome was reduced by appointing the independent review panel to assess the potential cases, against a specific criteria list (Appendix 2.4). Recall bias was minimised by requesting the controls soon after the anaesthetic was undertaken, such that both case and control questionnaires would have been completed in the immediate days after the event whilst still fresh in the minds of those completing the questionnaires (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Hence efforts to minimise misclassification were made, and if they occurred the likelihood was that they were primarily non-differential in nature and at worse biased the measured odds towards unity (i.e. underestimate associations).

The issue of missing data in the case-control study was a concern (Breslow and Day 1980; Katz 1999). Efforts were made at the study conduct stage to minimised missing data, but some data remained unknown and at the univariable level, separate categories for unknown values were created for categorical variables, allowing inclusion of this data and assessment of potential associations of the unknown categories with outcome (Katz 1999). In the multivariable model building process, independent variables with large numbers of missing values were only considered in the multivariable analysis if of major biological importance. For some variables, the approach of value estimation was employed (Katz 1999), when the actual value was unknown but a specific category was confidently estimated (e.g. age in cats). Finally, the final multivariable models were reported with the number of missing values stated (Breslow and Day 1980; Schlesselman 1982; Katz 1999).

The logistic regression and the conditional logistic regression approaches were efficient methods of assessing multiple explanatory variables and adjusting for confounding and effect modification (Dohoo, Martin et al. 2003). Preliminary univariable assessment and exploratory stratification allowed increased understanding of the data and helped

identify a rational approach to the subsequent process of building the multivariable model (Hosmer and Lemeshow 2000). Methods of assessing model fit included goodness-of fit tests and residual diagnostics though in the matched study in rabbits model assessment was more difficult (Hosmer and Lemeshow 2000). The Hosmer-Lemeshow goodness-of-fit test statistic is a useful test for assessing model fit, though it is reported to have a low sensitivity, and Hosmer and Lemeshow (2000) recommend combining this test with diagnostic statistics that assess model fit and influence of individual observations. These methods were employed and the fit of models were reported. Further validation of the models, could also have been performed. External methods of model validation are important to models predicting prognosis or diagnosis of disease but are less relevant for studies identifying prognostic factors associated with an outcome whilst adjusting for confounders, such as the current study, and hence were not undertaken (Katz 1999; Dohoo, Martin et al. 2003).

In summary, the nested case-control study was an efficient method to assess anaesthetic-related death. Issues of selection bias related to non-response were a particular concern of this method, but were minimised in the study design and quantified in the data collection period. The logistic regression approach was a powerful method of analysis for these datasets of moderate size and allowed a comprehensive evaluation of major risk factors for anaesthetic-related death.

Chapter 3: Practice Characteristics and Anaesthetic Management

3.1 Introduction

Anaesthetic drugs available for small animals in the UK have changed over the last twenty years since the last UK study (Clarke and Hall 1990). Work in other countries (Wagner and Hellyer 2000; Nicholson and Watson 2001) suggests anaesthesia in veterinary practice has followed suit, this has not been established in the UK. The aims of this chapter were to describe the cohort in terms of the type of practices and the facilities available, the patient management routinely undertaken, the anaesthetic agents commonly used and the perceived risks of anaesthetic-related death.

3.2 Materials and Methods

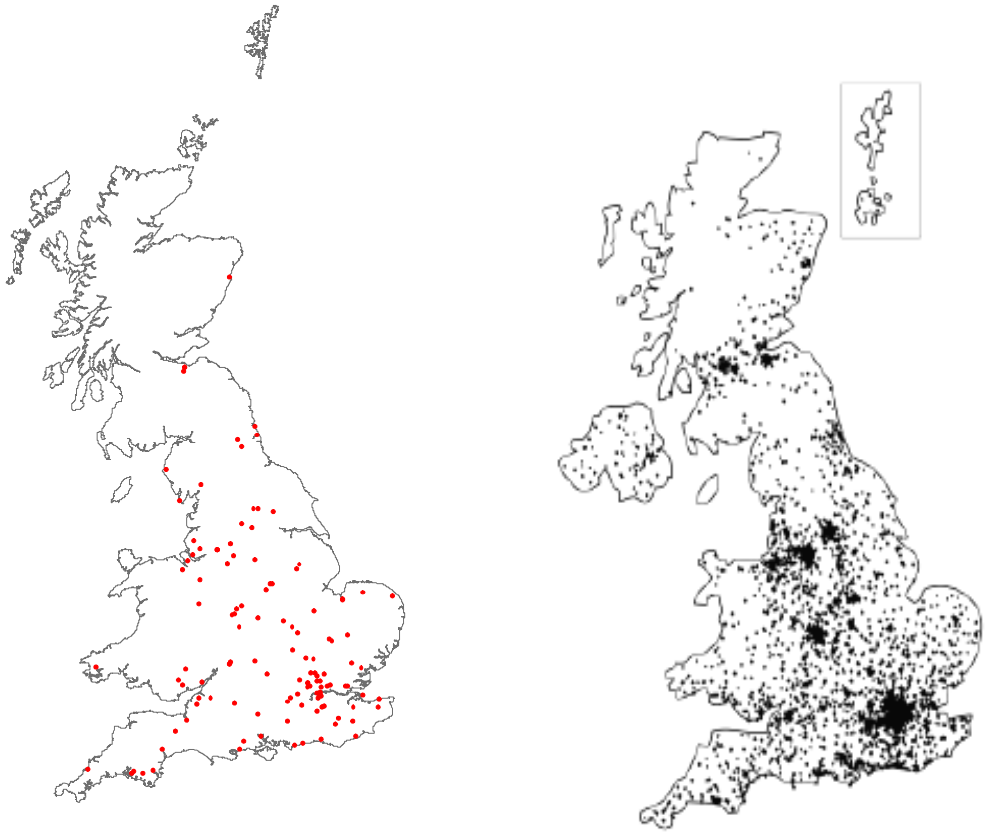
A 3-page questionnaire was developed and tested (Appendix 2.7, Chapter 2). This was administered to all participating centres during the study period. Practices that were visited had the questionnaire administered face-to-face by the primary investigator to the organising contact at the centre. All other centres received a postal version of the same questionnaire and this was followed up by a telephone interview if the posted version was not returned. Follow up checks where data were missing were undertaken by telephone. All data were entered into a relational database (Access 2000, Microsoft) and then exported to statistical software (Stata 7.0, Statacorp) to allow descriptive statistics to be compiled. Mean and standard deviations were reported unless the data appeared non-normally distributed, as assessed by graphical methods, and then median and interquartile ranges were reported (Kirkwood 1988). When assessing the number of centres using specific factors the number of centres and percentage of participating centres was reported. Estimated yearly species-specific caseloads were based on the estimated weekly totals multiplied by 52. Confidence intervals were calculated for proportions as described by Kirkwood (1988).

3.3 Results

One hundred and eighteen centres participated in the study, and one centre was excluded that was outside the UK. All centres completed a practice survey. Seventy-three completed the questionnaire through a face-to-face interview with the contact

veterinary surgeon or nurse (62% of non-excluded centres), and 44 completed the questionnaire by self-administration (38%). Centres in the UK were predominately located in England (Figure 3.1), but included practices from Jersey to Aberdeen, five of the six UK veterinary schools, and one other referral institution (the Animal Health Trust).

Figure 3.1 Distribution of practices in the UK



a. CEPSAF Study population practices

b. RCVS distribution of UK (RCVS 2004)

3.3.1 Practice Characteristics

Eighty-three practices (71%) were described as small animal practices and at least approximately 95% of their work, based on veterinary surgeon time, was small animal work. There were 28 practices (24%) that were classified as mixed, undertaking small animal, equine and farm animal work, and there were a further 6 centres (5%) termed veterinary schools or veterinary institutions. The practices were additionally

classified as RCVS hospitals (see www.rcvs.org.uk) for 44 centres (38% of all centres), and BSAVA standard practices (see www.bsava.org.uk) for 17 practices (14%). The median percentage of first opinion work as opposed to referral work was 99% (interquartile range 95-100%), whilst the majority of veterinary institutions undertook less than 25% first opinion work (Table 3.1).

Table 3.1 The amount of first opinion work by centre

Percent First Opinion	**Small Animal**	**Mixed Practice**	**Veterinary Institution***	**Total** (% of total)**
0- 24 %	1	0	5	6 (5%)
25 – 49 %	1	0	0	1 (1%)
50 – 74%	5	0	1	6 (5%)
75 – 100%	76	28	0	104 (89%)
Total	83	28	6	117

* Veterinary institution includes veterinary schools and one veterinary referral institution.

The majority of practices had between 3 and 6 veterinary surgeons undertaking small animal work with a median of 4 (range 1-42), whilst veterinary institutions had a median of 23 (range 13-42 veterinary surgeons, Table 3.2). Of these veterinary centres, 67 (57%) had no general certificate holders (i.e. RCVS certificate in subjects other than anaesthesia), 23 (20%) of the centres had one general certificate holder, 21 (18%) had 2-4 certificates and 6 had 5 or more (5%, i.e. the veterinary institutions). Six practices had a diploma holder (i.e. RCVS diploma in subjects other than anaesthesia, 5%) and 2 (2%) had three to four diploma holders, all veterinary institutions had more than four diploma holders. Nine practices (8%) had one or two certificate holder in veterinary anaesthesia and five practices (4%) had a diploma holder in veterinary anaesthesia, whilst all veterinary institutions had certificate and diploma holders in veterinary anaesthesia. The veterinary centres had a median of three qualified veterinary nurse (interquartile range 1- 5) and a median of three training or non-qualified nurses (interquartile range 2- 4) undertaking small animal work.

Table 3.2 Number of veterinary surgeons per centre

Number of Veterinarians	Small Animal	Mixed Practice	Veterinary Institution*	Total (% of Total)
1- 2	20 (24%)	2 (7%)	0	22 (19%)
3 - 4	34 (41%)	12 (43%)	0	46 (39%)
5 - 6	18 (22%)	12 (43%)	0	30 (26%)
7 - max	11 (13%)	2 (7%)	6 (100%)	19 (16%)
Total	83	28	6	117

* Veterinary institution includes veterinary schools and one veterinary referral institution.

Emergency cover was provided by the same centre for 73 clinics (62%), was shared with another practice for 24 practices (21%), and by an emergency clinic for 20 practices (17%). Seventy-eight centres (67%) had a nurse or veterinary surgeon present on the premises 24 hours a day, one had a veterinary student on the premises 24 hours a day, and 38 (32%) did not have personnel on site 24 hours a day.

3.3.2 Anaesthetic and Sedative Agents Used

Dogs and cats presenting for sedation (not anaesthesia) were most commonly sedated with medetomidine combinations (Table 3.3). Acepromazine was the next most commonly used agent for sedation, followed by benzodiazepines, often with an opioid in dogs or ketamine in cats. Other agents infrequently used for sedation, included ketamine combinations in dogs (6 clinics, 5%), and xylazine combinations in cats (1 clinic, 1%). The opioids most commonly used in dogs for sedation, were butorphanol (79 centres, 68%), buprenorphine (19 centres, 16%), pethidine (9 centres, 8%), morphine (6 centres, 5%) and methadone (3 centres, 3%). In cats, the opioids most commonly used were butorphanol (66 centres, 56%), buprenorphine (15 centres, 13%), pethidine (5 centres, 4%), morphine (3 centres, 3%), and methadone (2 centres, 2%).

Table 3.3 Sedation agents commonly used in dogs and cats

Sedation combinations*	**Dogs**	**Cats**
Acepromazine combinations	44 (38%)	30 (26%)
Medetomidine combinations	98 (84%)	93 (79%)
Benzodiazepine / opioid combinations	6 (5%)	25 (22%)
Other sedatives	6 (5%)	1 (1%)

* Drug combinations are not mutually exclusive, number of centres and percent of 117.

Premedication of patients prior to anaesthesia was generally undertaken with acepromazine combinations in dogs and cats (Table 3.4). Over 90% of centres regularly used acepromazine for premedication in dogs and cats. This was followed by medetomidine and benzodiazepines in both species. Four centres did not routinely premedicate cats prior to anaesthesia. Eight centres regularly used atropine as a premedication in cats (7%). The opioid most commonly used at premedication in dogs was buprenorphine (70 centres, 60%), but butorphanol (25 centres, 21%), pethidine (23 centres, 20%), morphine (15 centres, 13%) and methadone (7 centres, 6%) were also used. Similar use of opioids was observed in cats at premedication, with 65 centres regularly using buprenorphine (56%), 22 butorphanol (19%), 18 pethidine (15%), 10 morphine (9%), and 5 methadone (4%).

Table 3.4 Premedication agents commonly used in dogs and cats

Premedication combinations*	**Dogs**	**Cats**
Acepromazine combinations	114 (97%)	99 (85%)
Medetomidine combinations	10 (9%)	18 (15%)
Benzodiazepine combinations	3 (3%)	4 (3%)
Xylazine combinations	0	2 (2%)
None	0	4 (3%)

* Drug combinations are not mutually exclusive. Number of centres and percent of 117.

Anaesthesia was most often induced with propofol in dogs and cats (Table 3.5). The next most commonly used agents were thiopentone in dogs and ketamine, thiopentone and Saffan in cats. Of those centres that regularly used propofol, 67 (of 113 centres regularly using propofol, 59%) used it in over 75% of their canine anaesthetics and 58 (of 102 centres, 57%) used it in over 75% of their feline patients. In contrast, only 13 centres (of 55 centres, 24%) and 5 centres (of 28, 18%) that regularly used thiopentone, used it in over 75% of their canine and feline patients respectively.

Maintenance of anaesthesia was primarily undertaken with isoflurane in both dogs and cats. One hundred and twelve centres (96%) used isoflurane regularly in dogs, and 114 centres (97%) in cats. Only 25 and 24 centres (21%) used halothane regularly in dogs and cats respectively. Eight centres (7% of centres) used sevoflurane in dogs and cats. Nitrous oxide was infrequently used in dogs and cats (32 clinics, 27%). Dogs were intubated at all centres, principally with cuffed endotracheal tubes. Cats were intubated regularly by 116 centres (99%), of which 44% of centres used cuffed endotracheal tubes, 25% used uncuffed tubes, and 26% used both cuffed and uncuffed tubes (4% of centres used tubes but did not specify if cuffed or uncuffed and for 1 centre it was not clear if they intubated cats).

Table 3.5 Induction agents commonly used in dogs and cats

Induction agents used*	**Dogs**	**Cats**
Propofol	113 (97%)	102 (87%)
Thiopentone	55 (47%)	28 (24%)
Ketamine combinations	2 (2%)	35 (30%)
Saffan	0	20 (17%)
Medetomidine (without ketamine)	2 (2%)	0
Mask induction	4 (3%)	7 (6%)

* Drug combinations are not mutually exclusive, number of centres and percent of 117.

Rabbits generally were anaesthetised with medetomidine and ketamine combinations or Hypnorm (a combination of fentanyl and fluanisone) (Table 3.6). Two centres did not anaesthetise rabbits. Most centres primarily used one or the other of the two

combinations, though 14 (12%) used both combinations regularly. Other combinations used for induction of anaesthesia included mask inductions, xylazine and ketamine, propofol (1 centre) and Saffan (1 centre). Maintenance of anaesthesia was with the injectable combinations or inhalation agents. Isoflurane was regularly used by 104 centres (89%), halothane by 7 (6%) and sevoflurane by 6 centres (5%). Sixty centres (51%) indicated they intubated rabbits, and 47 centres (40%) did not intubate rabbits (10 centres did not give this information).

Table 3.6 Injectable anaesthetic agents commonly used in rabbits

Anaesthetic agents used*	**No. of Centres**
Medetomidine and ketamine	88 (75%)
Hypnorm +/- benzodiazepines	22 (19%)
Mask induction	17 (15%)
Xylazine and ketamine	5 (4%)
Other	2 (2%)

* Drug combinations are not mutually exclusive, number of centres and percent of 117.

Anaesthetic circuits commonly used included the Circle, used regularly by 88 centres (75%), the T piece (102 centres, 87%), the Lack (55 centres, 47%) and the Bain (40 centres, 34%). The Magill was used regularly by 21 clinics (18%) and the Humphrey's ADE was regularly used by 29 centres (25%). Ventilators were owned by 26 centres (22%), of which 13 (11%) used them regularly.

3.3.3 Perioperative Patient Management and Monitoring

Preoperative screening blood tests were undertaken in a median of 30% of dogs and cats at the centres (interquartile range 15-50%), with 62 (52%) centres routinely performing biochemical tests only, and 46 (39%) centres doing both biochemical and haematological tests (7 (6%) centres did not specify the tests performed, and one centre did not undertake preoperative blood tests). Intravenous catheters were routinely used in dog and cat patients in 33 and 25 centres respectively (28% and 21% respectively). Eight centres (7%) reported they routinely used intravenous fluids in dogs and cats, whilst the remainder stated they used them principally for high-risk patients, old

patients and when procedures were anticipated to be long. The majority of centres routinely weighed dogs (115 centres, 98%) and cats (107 centres, 92%). Premedication and sedation of patients was undertaken by both veterinary nurses and veterinary surgeons at most clinics, though induction of anaesthesia was performed by only the veterinary surgeon at 93 centres (79%). Twenty-three centres indicated the veterinary nurse also induced anaesthesia (20%), and one centre did not specify who induced anaesthesia.

Monitoring of anaesthesia was generally undertaken by a veterinary nurse, with only 3 centres (3%) routinely having a veterinary surgeon monitor the anaesthetics. Written records of anaesthesia were routinely undertaken at 49 (42%) clinics, occasionally used at 51 (43%) and never at 14 (12%) of the centres. Equipment available and used for routine monitoring of anaesthesia of dogs and cats varied across the centres. Oesophageal stethoscopes were routinely used to monitor anaesthesia at 96 (82%) clinics, with only two centres not having one. Pulse oximeters were owned by 93 centres (79%) and 84 (72%) used them routinely. Ninety-five clinics (81%) were able to monitor a patient's electrocardiogram, but only 20 (17%) routinely did so. Similarly, 56 centres (48%) had non-invasive arterial blood pressure monitoring facilities but only 23 (20% of all centres) used them regularly. Only 7 centres (6%) monitored direct arterial blood pressure and only 5 (4%) of these did this regularly. Capnography was available at 26 centres (22%) of which 24 used it (21%) regularly and 18 (15%) centres indicated they monitored patient temperature of which 4 did this routinely (3%).

3.3.4 Centres' Perceptions of Risk and Caseload

The estimated median weekly caseload of anaesthetics and sedations, at the time the centres completed the questionnaire, was 20 dogs (interquartile range (IQR) 13–30, range 3-125), 20 cats (IQR 12–30, range 5-80) and 3 exotics patients (IQR 2–5, range 0-20). In the previous year, practices estimated they had a median of 0 anaesthetic-related deaths in dogs (IQR 0-1, range 0-10), in cats a median of 0 (IQR 0-1, range 0-10), and in exotics a median of 0 (IQR 0-2, range 0-8). For those centres that estimated the number of anaesthetic deaths that occurred over the last year (101 centres), the perceived caseloads over 1 year (based on their current estimated caseloads) were 143,416 dog, 129,272 cat and 21,424 exotics anaesthetics (Table 3.7). The perceived number of anaesthetic-related deaths was 90 dogs, 80 cats and 125 exotic patients.

These resulted in anaesthetic-related risks of approximately 0.063% in dogs, 0.062% in cats and 0.58% in exotics.

Table 3.7 Risks of anaesthetic-related death as estimated by the individual centres

Species	Events per Year	Number of Deaths	Risk (95% Confidence Interval)
Dog	143,416	90	0.063% (0.050 – 0.076%)
Cat	129,272	80	0.062% (0.048 – 0.075%)
Exotics	21,424	125	0.58% (0.48 – 0.69%)

3.4 Discussion

The survey of practices highlighted a number of trends in practice anaesthetic management. There was a broad range of types of practices and number and qualifications of personnel working in the centres. Anaesthetic drug use was similar across the practices. Patient monitoring was routinely undertaken but was often superficial and few centres routinely provided perioperative fluid support. The perceived risk of anaesthetic-related death was low.

The geographical distribution throughout the UK was similar to that of the overall density of UK practices (RCVS 2004)(Figure 3.1) with most centres in England. The size of the cohort reflected a broad range of practice types. One hundred and eleven practices (excluding the 6 veterinary institutions) represented approximately 5.5% of all UK practices (based on an estimate of 2000 practices)(RCVS 2000). The 14% of this study cohort that were classified as BSAVA standard practices was similar to the 12% of all UK practices (248 of 2000)(BSAVA 2004). However the number of hospitals involved (37%) was much higher than the approximate 5% of all UK practices (BSAVA 2004), and reflects the decision to actively recruit hospitals to the study (see Chapter 2). The higher percent of small animal practices (70% of centres), as compared to mixed practices, compared to the 49% of all UK practices (RCVS 2004) was to be expected given that this was a study of small animals.

The mean number of veterinary surgeons per practice (mean 5.4, median 4) appeared higher than the mean value of 4.2 for the UK (RCVS 2000), though was similar when veterinary institutions were excluded (mean 4.2, median 4). The number of RCVS diploma holders in practice was broadly similar in this cohort to the UK (3% for this study and for the UK (RCVS 2000)). After excluding veterinary institutions, the number of veterinary surgeons with a RCVS certificate was however higher than the UK average: approximately 19% of the cohort had a certificate compared to 7% of UK veterinary surgeons in practice (RCVS 2000). It is likely this study would attract the more motivated members of the profession and such a group of professionals would be more likely to have gained further qualifications. The median number of nurses (including unqualified nurses) per practice of 5.6 (excluding veterinary institutions) was comparable to the UK mean of 5.8 per practice (RCVS 2000). On the basis of these indices of practice size and type, the practices were generally comparable to UK practices as a whole, although there was a tendency to more veterinary surgeons having further qualifications in this cohort.

The use of anaesthetic drugs was broadly similar across practices. Sedation was principally undertaken with medetomidine combinations in dogs and cats. Medetomidine was not available in the last UK study (Clarke and Hall 1990), though since its introduction it has become popular due to its consistent and profound dose-dependent sedation and the presence of a specific antagonist (Cullen 1996). This was similar to work in the USA where 171 of 333 practices regularly used medetomidine (Wagner and Hellyer 2000).

Premedication in dogs and cats was primarily undertaken with acepromazine combined with an opioid. This was similar to trends in international studies (Dyson, Maxie et al. 1998; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001), and in part may reflect the previously reported reduced risk associated with acepromazine compared particularly to xylazine use (Clarke and Hall 1990; Dyson, Maxie et al. 1998). Cats were more often premedicated in this study than reported in previous surveys (12 - 30% of practitioners did not routinely premedicate cats in previous studies, compared to 3% in this study)(Dodman and Lamb 1992; Joubert 2000; Nicholson and Watson 2001). Alpha$_2$ agonists were the next most common group of sedatives used for premedication and this was similar to previous reports (Joubert

2000; Wagner and Hellyer 2000; Nicholson and Watson 2001). Earlier studies tended to report greater use of xylazine than the more recently released medetomidine. Opioids were routinely administered preoperatively in both species by participating clinics. This is in contrast to work reporting use of analgesics in UK practice in dogs and cats, where many veterinary surgeons did not routinely used perioperative opioids particularly in cats (Capner, Lascelles et al. 1999; Lascelles, Capner et al. 1999). That more centres reported routine use of opioids may reflect changes since these publications (i.e. 5 years) or a more anaesthetic and analgesic aware population of centres taking part in this current study.

Induction agents used changed substantially since the last UK study (Clarke and Hall 1990). Since this study, propofol was introduced to the UK veterinary market, and now represents the most commonly used induction agent. The rapid recovery properties and lack of perivascular irritancy (Hall, Clarke et al. 2001), combined with its increasingly comparable cost to thiopentone (originally it was much more expensive), have helped increase its popularity. There has been a perception in veterinary practice that propofol represents a safer drug than thiopentone, inducing less cardiopulmonary depressant effects (Wagner, Wright et al. 2003), when experimental evidence suggests similar effects to thiopentone (Quandt, Robinson et al. 1998). Propofol use in the current study contrasted to international studies where thiopentone remained more commonly used than propofol in dogs and Saffan and ketamine / alpha$_2$ agonist combinations in cats (Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001). Mask inductions were relatively rare. This was comparable to more recent studies (Joubert 2000; Nicholson and Watson 2001), though was lower than earlier studies where 10-20% of centres routinely used mask inductions in dogs and cats (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998). The trends away from mask inductions was comparable with other more recent studies, the increasing use of propofol in dogs and cats was a new trend and may reflect that previous studies were undertaken 5 years or more ago.

Maintenance of anaesthesia by centres was principally undertaken with isoflurane and only 20% of centres regularly used halothane in dogs and cats. Sevoflurane has been recently introduced to UK practice and just less than 10% of centres were now regularly using it in dogs and cats. This trend was comparable to an American study (Wagner

and Hellyer 2000) where isoflurane was the main maintenance inhalation agent, though was in contrast to other recent studies from Australia and South Africa (Joubert 2000; Nicholson and Watson 2001) and earlier studies where halothane was the main inhalation agent used (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998). Endotracheal intubation was routinely performed by nearly all centres in dogs and cats, and this was in contrast to other recent work where cats were less commonly intubated (Wagner and Hellyer 2000; Nicholson and Watson 2001). Cats are technically more difficult to intubate (Hall and Taylor 1994) and previous studies have identified a higher risk associated with intubation of cats (Clarke and Hall 1990; Dyson, Maxie et al. 1998). It could be expected some practitioners would be reluctant to intubate cats, but this was not observed in the present study.

The trend for centres to use one anaesthetic combination exclusively was a particular feature of rabbit anaesthesia and reflected the limited drugs with market authorisation in rabbits and possibly a lower level of anaesthetic expertise in this species. Hypnorm was available in the last UK study but medetomidine with ketamine and isoflurane were not (Clarke and Hall 1990). Intubation of rabbits was less commonly performed than in dogs and cats and this reflected the greater technical difficulty in intubating a species where visualisation of the vocal fold under anesthesia is difficult and the airways are small (Flecknell 1996).

Anaesthetic circuit use in this study was different to that seen in the last UK study where the To-and Fro and T Piece circuits were commonly used (Clarke and Hall 1990). Here the Circle and T piece were commonly used with a smaller number of centres using other non-rebreathing circuits (i.e. the Bain, Magill, Lack) and the newer combination circuit, Humphrey's ADE. This is similar to trends elsewhere (Nicholson and Watson 2001) and the Circle has become popular for patients over 5-10 kg, because of its more predictable performance compared to the To-and Fro with greater gas efficiency compared to non-rebreathing circuits (Hall, Clarke et al. 2001). The use of lower flow circuits, such as the Circle, has become popular with the introduction of the more expensive agents isoflurane and sevoflurane.

Preoperative blood testing was generally reserved for patients perceived to be at a greater anaesthetic risk, though some centres routinely offered preoperative blood tests to all anaesthetic patients. This was comparable to previous international work

(Nicholson and Watson 2001). Intravenous catheters were not routinely placed by most centres, and though similar to previous work (Wagner and Hellyer 2000), this was cause for concern as perioperative venous access was not immediately available in most centres. Similarly, intravenous fluid therapy was not routinely provided. Though for most patients, anaesthesia was induced by a veterinary surgeon, a number of centres indicated that nurses also routinely induced anaesthesia. Under the Veterinary Surgeons Act 1966, anaesthesia is considered an act of veterinary surgery and as such a veterinary surgeon should supervise the anaesthetic. Hence, though not required for induction of anaesthesia, a veterinary surgeon should be present for active and continuous supervision and it remained unclear from the questionnaire if this were the case.

Patient monitoring during anaesthesia was generally undertaken by a dedicated veterinary nurse, as one recent study also reported (Nicholson and Watson 2001). This appears an improvement since the last UK study, when 20% of practices did not use a separate person to monitor the anaesthetics (Clarke and Hall 1990). Written anaesthetic records were not routinely made by many of the centres, and though it may not have reduced the standard of care, in an increasingly litigious environment, this may become a cause for concern. The level of written recording was comparable to one study that evaluated it (Joubert 2000). General standards of electronic monitoring were limited. Clinical patient assessment was routinely undertaken by most centres, but other monitoring devices were less frequently employed. Oesophageal stethoscopes were commonly used though these give little additional information over clinical patient assessment. Pulse oximeters were routinely used by many centres, more so than in other recent reports (Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001). However, arterial blood pressure measurement, capnography and electrocardiography were not regularly used even when a substantial number of centres had these monitors. The level of use of these additional monitors was similar to that reported elsewhere (Dyson, Maxie et al. 1998; Joubert 2000; Nicholson and Watson 2001). Temperature monitoring was infrequently undertaken even though very simple. The standards of monitoring reported were likely to limit the ability of many practices to detect minor complications before they become major.

The perceived anaesthetic mortality risk in dogs and cats, i.e. 0.06%, was similar to other studies employing similar retrospective single questionnaire methodology

(Dodman and Lamb 1992; Joubert 2000). How accurate these retrospective figures were, is difficult to assess, but they will be compared to this study's results (Chapter 4).

The response rate was good in this study and reflects the fact that centres participated in the study for a period of time and had repeated contact with the primary investigator. Ideally face-to-face interviews would have been undertaken for all centres by one investigator or a small number of trained investigators to increase consistency of questionnaire administration (Dohoo, Martin et al. 2003). However, time constraints made this particularly difficult for the geographically distant centres. That a number completed the same questionnaire by post could have affected the consistency of replies, though questions were designed to be reasonably self-explanatory and they had been tested on practitioners and veterinary epidemiologists prior to the study. The postally administered questionnaires had more data omissions and these were amended by follow-up telephone questionnaires to increase the completeness of the dataset. In general, due to the simplicity of most questions, the responses should have been reasonably consistent across methods of administration. How generalisable the results are to the UK population remains unclear though the indices of practice size would suggest they are comparable albeit with a slight bias towards more motivated centres.

In summary, the trends in anaesthesia are comparable to other recent studies with improvement being made to standards since the last UK study 20 years ago (Clarke and Hall 1990). Monitoring standards have improved but appear to warrant further changes and intravenous catheterisation and fluid support could also be improved.

Chapter 4: Risks of Anaesthetic-Related Death in Small Animals

4.1 Introduction

The risks of anaesthetic-related death in small animals have not been quantified in the UK for 20 years. Approximately 1 in 434 dogs and 1 in 340 cats were reported to die of anaesthetic-related death in the last UK study (Clarke and Hall 1990). In subsequent international studies the risk in general practice has been estimated at nearer 1 in 1000 dogs and cats (Dodman and Lamb 1992; Rintasalo and Vainio 1995; Dyson, Maxie et al. 1998; Joubert 2000). Risks of anaesthetic-related death remain poorly documented for other small animal species. The aim of this section was to estimate the risk of anaesthetic-related death in small animal species.

4.2 Materials and Methods:

4.2.1 Case Definition and Study Population

Anaesthetic-related death (a Case) was defined as a perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death or euthanasia was due solely to inoperable surgical or pre-existing medical conditions (Chapter 2). A death was considered a case if anaesthesia could not be reasonably excluded as a contributory factor. Cases were identified by the participating centres in the first instance and subsequently by the investigators from the cohort of anaesthetics recorded by each practice. Deaths recorded in the cohort, but for which no case-control questionnaire was submitted by the clinic, were investigated and a case-control questionnaire was requested if the death could be considered a case. Case-control questionnaires were requested for all potential cases in all small animal species (dogs, cats and exotics) to allow for estimation of risks of anaesthetic-related death.

The classification of dog and cat cases was undertaken by an independent review panel. Potential cases were assessed based on the case definition and a set of documented criteria **(**Appendix 2.4) and the cause of death of cases was classified against a further set of criteria (Appendix 2.5). Case selection and cause of death for other small animal

species followed the same procedure as in the dogs and cats, though the primary investigator classified the cases (Appendix 2.4).

The study population consisted of all small animals anaesthetised and sedated at the veterinary centres during their participation in the study.

4.2.2 Data Collection Methods

All anaesthetic and sedation events occurring at participating centre were recorded prospectively as self-administered questionnaires by the centres and returned on a monthly basis (Appendix 2.2). One line entries were recorded for each patient anaesthetised or sedated at the participating centres in these case diary forms. The unique centre code, date of procedure, patient identification number or name, species, whether it received an anaesthetic or sedation, and outcome at 48 hours (recorded as alive, dead or euthanased) were recorded for each patient. Brief details of the reason for death or euthanasia were recorded in the diary for patients that died. Anaesthesia was defined as chemical restraint, sufficient to allow endotracheal intubation (independent of whether endotracheal intubation was performed). Sedation was defined as chemical restraint insufficient to allow endotracheal intubation.

4.2.3 Analysis

Risks for anaesthetic-related death were calculated by species, by dividing the total number of cases for that species by the total number of patients of the species anaesthetised. Ninety-five percent confidence intervals were calculated based on the standard normal distribution, when there were 10 or more cases and non-cases as described by Kirkwood (1988). When smaller samples were present, exact confidence intervals, based on the binomial distribution, were calculated (Dohoo, Martin et al. 2003). Differences between risks in dogs, cats and rabbits were compared using the Chi-squared test followed by a post-hoc normal test to compare two proportions (Kirkwood 1988).

Species-specific clinic-level risks of anaesthetic-related death were additional recorded and compared by practice type and practice standard. Practice types, derived from the practice survey (Chapter 2), were classified as small animal practices if they did more than 95% small animal work based on veterinary surgeons time, mixed if they did

95% or less small animal work, and veterinary institution if they were a veterinary school or non-veterinary school institution (i.e. the Animal Health Trust). Practice standards were classified by the RCVS hospital and the BSAVA practice standard schemes (see www.bsava.org.uk and www.rcvs.org.uk), and were categorised as RCVS Hospital, BSAVA standard, or neither. Veterinary institutions as defined under practice type were excluded from this second classification due to their differing patient and procedural populations and differing risks. Clinic-level risks were reported as median and interquartile ranges and were compared by practice type and practice standard using the Kruskal Wallis test (Kirkwood 1988).

Species specific risks for healthy (ASA 1-2) and sick (ASA 3-5) patients (see Appendix 2.1) were calculated from the number of cases in each health-status category divided by the estimated of the number of patients anaesthetised in that health status category. The number of patients anaesthetised in each health-status stratum was calculated from the proportion of the controls from the case-control study (see Chapter 2) in the specific category, multiplied by the total number of anaesthetics and sedations undertaken during the study period.

Health status risk = Number of Cases in the Health status stratum / (number of patients anaesthetised) x (number of controls of that health status/total number of controls)

Ninety-five percent confidence intervals were calculated for health status risks based on the standard normal distribution and within species differences in risk by health status were compared with the normal test for proportions (1988). Cause of death was reported for dogs, cats and rabbits and the timing of death as reported on the case-control questionnaires was documented. Postoperative deaths in dogs, cats and rabbits were additionally categorised by there time from termination of anaesthesia to death of euthanasia.

4.3 Results:

One hundred and eighteen centres participated in the study and one centre was excluded for being outside the UK. Centres participated for a mean duration of 15 months (standard deviation 6.6 months) with a range of 2 to 25 months. During this time 98,036 dogs, 79,178 cats and 8,209 rabbits were anaesthetised and sedated (Table 4.1). The

perioperative mortality risks (all cause) were approximately 0.3% died and 1.5-1.7% euthanased in dogs and cats, and in rabbits 1.8% died and 2.6% were euthanased (Table 4.1). The risks were significantly greater in rabbits than dogs or cats (P<0.001), and the risk of euthanasia was greater in cats than dogs (P=0.03). The risk of anaesthetic-related death was significantly greater in rabbits than cats or dogs and the risk in cats was significantly higher than in dogs (Dogs 0.17%, Cats 0.24%, Rabbits 1.39%, P<0.001) (Table 4.2). Risks of anaesthetic-related death for other small animal species were higher with larger confidence intervals than in dogs and cats and ranged from 0.33% in ferrets to 16.33% in budgerigars (Table 4.2).

Estimated risks for healthy patients (ASA 1-2) were of 0.05% for dogs, 0.11% for cats and 0.73% for rabbits (Table 4.3). The risks in sick patients were significantly higher than in health patients (P<0.0001). Risks for sick patients (ASA 3-5) were 1.33% for dogs, 1.40% for cats and 7.37% for rabbits.

Median anaesthetic-related risks by practice type in dogs were 0.12% for both small animal and mixed practices, and 0.31% for veterinary institutions (Table 4.4). In cats, the median risks were higher than in dogs and were 0.19% for small animal practices, 0.14% for mixed practices, and 0.60% for veterinary institutions. Median risks in rabbits were 0.79% for small animal practices, 0% for mixed practices, and 3.53% for veterinary institutions. Median risks for different practice standards in dogs were lowest for those not classified as a Hospital or BSAVA standard (Table 4.5). In cats, the median risks were 0.16% for RCVS Hospitals, 0.19% for BSAVA standard, and 0.19% for practice classified as neither. In rabbits, the risk was higher for practices being neither Hospital nor BSAVA standard. Within species risks were not significantly different between practice types or standards.

Table 4.1 Risk of death in small animals

Species	Number at Risk	Total Deaths	Risk of Death (95% CI)	Total Euthanased	Risk of Euthanasia (95% CI)
Dog	98,036	285	0.29% (0.26 – 0.32%)	1,496	1.53% (1.45 – 1.60%)
Cat	79,178	248	0.31% (0.27 – 0.35%)	1,306	1.65% (1.56 – 1.74%)
Rabbit	8,209	146	1.78% (1.49 – 2.06%)	214	2.61% (2.26 – 2.95%)
Guinea Pig	1,288	63	5.13% (3.90 – 6.36%)	65	5.29% (4.04 – 6.55%)
Ferret	600	4	0.67% (0.18 – 1.70%)**	12	2.00% (0.88 – 3.12%)
Hamsters	246	12	4.88% (2.19 – 7.57%)	30	12.20% (8.11 – 16.28%)
Chinchilla	334	11	3.29% (1.38 – 5.21%)	18	5.39% (2.97 – 7.81%)
Rat	398	7	1.76% (0.71 – 3.59%)**	25	6.28% (3.90 – 8.67%)
Other Small Mammals	232	7	3.02% (1.22 – 6.12%)**	20	8.62% (5.01 – 12.23%)
Budgerigar	49	11	22.4% (10.77 - 34.13%)**	3	6.12% (1.28 – 16.87%)**
Parrot	127	5	3.94% (1.29 – 8.95%)**	4	3.15% (0.86 – 7.87%)**
Other Birds	284	10	3.52% (1.38 – 5.66%)	19	6.69% (3.78 – 9.60%)
Reptiles	134	4	2.99% (0.82 – 7.47%)**	6	4.48% (1.66 – 9.49%)**
Other	50	2	4.00% (0.49 – 13.71%)**	3	6.00% (1.26 – 16.55%)**

* 95% Confidence interval, **Exact 95% Confidence Interval.

Table 4.2 Anaesthetic-related risk of death in small animals

Species	Number at Risk	Number of Anaesthetic-Related:			Risk of Anaesthetic related death / euthanasia (95% CI*)
		Deaths	Euthanased	Total Fatalities	
Dog	98,036	154	9	163	0.17% (0.14 – 0.19%)
Cat	79,178	179	10	189	0.24% (0.20 – 0.27%)
Rabbit	8,209	111	3	114	1.39% (1.14 – 1.64%)
Guinea Pig	1,288	48	1	49	3.80% (2.76 – 4.85%)
Ferret	601	2	0	2	0.33% (0.04 – 1.20%)**
Hamsters	246	9	0	9	3.66% (1.69 – 6.83%)**
Chinchilla	334	11	0	11	3.29% (1.38 – 5.21%)
Rat	398	7	1	8	2.01% (0.87 – 3.92%)**
Other Small Mammals	232	4	0	4	1.72% (0.47 – 4.36%)**
Budgerigar	49	8	0	8	16.33% (7.32 –29.66%)**
Parrot	127	5	0	5	3.94% (1.29 – 8.95%)**
Other Birds	284	5	0	5	1.76% (0.57 – 4.06%)**
Reptiles	134	2	0	2	1.49% (0.18 – 5.29%)**
Other	50	0	0	0	0% (0 – 7.11%)**

* 95% confidence intervals (95% CI). **Exact 95% Confidence Interval.

Table 4.3 Risk of anaesthetic-related death in healthy and sick dogs, cats and rabbits

Species	Health status*	Cases	Controls (% of total)	Estimated number of Anaesthetics per stratum	Risk of Anaesthetic related death	95% CI**
Dog	Healthy ASA 1-2	49	450 (92%)	90,618	0.05 %	0.04 – 0.07 %
	Sick ASA 3-5	99	37 (8%)	7,418	1.33 %	1.07 – 1.60 %
Cat	Healthy ASA 1-2	81	508 (92%)	72,473	0.11 %	0.09 – 0.14 %
	Sick ASA 3-5	94	47 (8%)	6,705	1.40 %	1.12 – 1.68 %
Rabbit	Healthy ASA 1-2	56	55 (93%)	7,652	0.73 %	0.54 – 0.93 %
	Sick ASA 3-5	41	4 (7%)	557	7.37%	5.20 – 9.54 %

*ASA 1-2: no/mild preoperative disease, ASA 3-5: severe preoperative disease. **95% confidence intervals.

Table 4.4 Clinic level risks of anaesthetic-related death by type of veterinary practice

Species	Small Animal Practice* (n= 82)	Mixed Practice* (n=28)	Veterinary institution* (n=6)
Dog	0.12% (0 – 0.31%)	0.12% (0 – 0.34%)	0.31% (0.10 – 0.39%)
Cat	0.19% (0 – 0.382%)	0.14% (0 – 0.25%)	0.60% (0.13 – 0.86%)
Rabbit	0.79% (0 – 2.33%)	0 (0 – 2.36%)	3.53% (1.44 – 5.21%)

*Median and interquartile ranges. Number of practices reported per stratum.

Table 4.5 Clinic level risks of anaesthetic-related death by practice standard

Species	**RCVS Hospital (n = 43)**	**BSAVA Standard (n = 17)**	**Neither (n = 50)**
Dog	0.12% (0 – 0.33%)	0.17% (0.11 – 0.34%)	0.08% (0 – 0.31%)
Cat	0.16% (0 – 0.33%)	0.19% (0.12 – 0.32%)	0.19% (0 – 0.38%)
Rabbit	0.63% (0 – 2.73%)	0 (0 – 1.52%)	1.06% (0 – 2.13%)

*Median and interquartile ranges. Number of practices are reported per stratum.

Table 4.6 Timing of death in Dogs, Cats and Rabbits

Timing of Death	**Dogs**	**Cats**	**Rabbits**
After Premedication	1 (1%)	2 (1%)	0
Induction of anaesthesia	9 (6%)	14 (8%)	6 (6%)
Maintenance of anaesthesia	68 (46%)	53 (30%)	29 (30%)
Postoperative death*	70 (47%)	106 (61%)	62 (64%)
0-3 hours postoperative	31 (44%)	66 (62%)	26 (42%)
3-6 hours postoperative	11 (16%)	9 (8%)	7 (11%)
6-12 hours postoperative	12 (17%)	7 (7%)	13 (21%)
12-24 hours postoperative	13 (19%)	12 (11%)	9 (15%)
24-48 hours postoperative	3 (4%)	10 (10%)	3 (5%)
Unknown time	0	2 (2%)	4 (6%)
Total	148 (100%)	175 (100%)	97 (100%)

*Postoperative deaths were additionally categorised by time after anaesthesia.

The postoperative period was a particularly common time for dogs, cats and rabbits to die. Over 60% of cats and rabbits, and nearly 50% of dogs died during this time period (Table 4.6) and of these postoperative deaths approximately half of the patients died within 3 hours of termination of the procedure. Cardiovascular and respiratory causes of death were the most common causes of death in dogs and cats with a substantial majority being of unknown cause (Table 4.7). In contrast most rabbits died of an unknown cause, with approximately 40% being of cardio-respiratory causes.

Table 4.7 Primary cause of death in dogs, cats and rabbits

Cause of Death	Dogs*	Cats*	Rabbits*
Cardio-Respiratory cause	109 (74%)	126 (72%)	38 (39%)
Neurological cause	7 (5%)	8 (5%)	2 (2%)
Renal	1 (1%)	6 (3%)	0
Unknown	31 (21%)	35 (20%)	57 (59%)
Total	148 (100%)	175 (100%)	97 (100%)

*Number of animals and percent of total. Only cases where a case-control questionnaire was received are included.

4.4 Discussion:

The risk of anaesthetic-related death appears to have substantially decreased from that reported in the last UK study and are comparable to more recent international studies (Clarke and Hall 1990; Dodman and Lamb 1992; Rintasalo and Vainio 1995; Dyson, Maxie et al. 1998; Joubert 2000). Given the relatively highly qualified population of veterinarians participating in the study compared to the level of qualifications documented by the RCVS in the UK (RCVS 2000)(Chapter 3), this estimate is likely to be an overestimate of the risk in the UK. From a comparisons perspective however this is likely to have been the case in the other studies reported, that is the most motivated practices and potentially the safest, participate in such studies. Both high-risk (ASA 3-5) and low-risk (ASA 1-2) patient risks have approximately halved over the twenty years since the last UK study. Case definition for healthy patients (ASA 1-2) in the last UK study was similar to that described in the current study with deaths classified as cases if the underlying disease / surgery could not explain the death, whilst in sick patients (ASA 3-5) all deaths were included (Clarke and Hall 1990). The results in healthy patients would be most comparable, whilst the risks in sick patients would be expected to be higher in the last study independent of major improvements in the standard of anaesthesia. The reduction in risk, particularly in healthy patients suggests changes in anaesthetic practice have resulted in improved safety of small animal anaesthesia. Since the last UK study, drugs such as isoflurane and medetomidine have

been introduced. Monitoring has improved and electronic monitors are more readily available (Wagner and Hellyer 2000; Nicholson and Watson 2001).

The risks reported were slightly higher than those described in recent international practice-based studies (Dodman and Lamb 1992; Rintasalo and Vainio 1995; Dyson, Maxie et al. 1998; Joubert 2000), though only in one of these studies was the definition of death stated or the percent healthy and sick patients within the study population reported (Dyson, Maxie et al. 1998). The definition was based on occurrence of perioperative cardiac arrest and was likely to represent only a proportion of anaesthetic-related perioperative deaths. The other studies were retrospective studies based on practitioners' recall of events over the previous 1 to 2 years, often with poor written documentation and without clear guidelines for the definition of anaesthetic death, and were more likely to underestimate the risk of death. All studies were based on smaller sample sizes and were likely to have larger confidence intervals. Hence, given the limits in these international studies' methodologies, the results suggest the standards of anaesthesia are comparable to international work.

In contrast, the risk of anaesthetic–related death in human anaesthesia consistently appears much lower. Studies evaluating deaths where anaesthesia played a contributory role, but was not the sole cause, were most comparable in terms of case definition and the risk documented was approximately 0.02 to 0.005% (Tikkanen and Hovi-Viander 1995; Eagle and Davis 1997; Suan, Perez-Torres et al. 1997; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001). That there should be such a difference was likely to reflect differences in standards of anaesthesia in human and veterinary anaesthesia more than species differences. Anaesthetist expertise and resources available in the medical setting are significantly greater than that routinely available in veterinary practice. Thus though standards have improved, there is substantial scope for further improvements.

Sick patients had a substantially higher risk of anaesthetic-death compared to healthy patients, as previous work reported (Clarke and Hall 1990; Dyson, Maxie et al. 1998), suggesting this group of patients remain a particular concern. Risks of greater than 1% in the ASA 3-5 patients highlight a population of patients in which small improvements could substantially reduce the risk of death. Risk factors associated with anaesthetic-related death in this group will be addressed in chapters 6 and 7. Comparing overall risks of death by species, the risks appeared to have reduced by a similar degree in

both dogs and cats, but not as dramatically as seen when reported by ASA status. This reflected changes in patient status of the population anaesthetised, with a trend to more sick patients being anaesthetised in the present study compared to the last UK study. Clarke and Hall (1990) reported approximately 4% of dogs and cats anaesthetised were ASA 3-5, whereas in the current study 8 to 9% of patients were higher risk (based on the proportion of controls being ASA 3-5, Table 2).

It is interesting to note the significant increased anaesthetic-related death risk reported in cats compared to dogs, particularly in lower risk patients (ASA 1-2). This agrees with the results of Clarke and Hall (1990) and Hosgood and Scholl (1998; 2002), but contrasts with work by Dodman and Lamb (1992) and Dyson and Pettifer (1997). These latter studies had smaller sample sizes and the lack of difference may have due to limited power of the studies to detect inter-species differences or to population differences. That apparently healthy cats (ASA 1-2) had a two-fold higher risk of death than healthy dogs, would suggest either preoperative assessment is poorer and more cats are misclassified as healthy when harbouring significant disease, or cats are at a greater risk of anaesthetic-related death. Recent work reported a prevalence of at least 7% of sub-clinical cardiac disease in apparently healthy cats (Cote, Manning et al. 2004), and if genuinely higher than that seen in dogs, undetected cardiac disease could contribute to the higher risk. Cats are reported to be prone to postoperative renal failure (Hall and Taylor 1994), and though the 48 hour postoperative follow up may have missed some of these cases, this species sensitivity also may have contributed to the higher risk. Cats are smaller than dogs in general and hence would be more prone to hypothermia, predisposing to prolonged recoveries and increased morbidity (Waterman 1981; Dhupa 1995; Kurz, Sessler et al. 1996). The reduced size might also predispose to overdosing of anaesthetics administered, particularly if patients were not weighed.

Endotracheal intubation has been associated with increased risk of death in cats but not dogs (Clarke and Hall 1990; Dyson, Maxie et al. 1998). It is technically more difficult and laryngospasm more likely in cats than dogs, predisposing to perioperative complications (Hall and Taylor 1994). Postoperative deaths were more common in cats than dogs (60% of deaths compared to 47% in dogs, Chapters 6 and 7), and some of these could have been related to difficult intubations and laryngeal swelling. Clarke and

Hall (1990) found that cats were also more likely to die postoperatively and suggested airway problems contributed.

The risks of other small animal species have been poorly documented and it is alarming to note the high risk of perioperative death reported in this study. Rabbits were the third most commonly anaesthetised species, and the risk of death was approximately 7 times greater than that reported for dogs (Table 1 and 2). With more than 8,000 rabbits being anaesthetised or sedated during the study and more than a hundred deaths, high risk can not be attributed to large confidence intervals and uncertainty of risk. Rabbits can exhibit stress on induction of anaesthesia, have a high surface-area to volume ratio predisposing to perioperative hypothermia, and have a predilection to preoperative diseases involving respiratory, digestive and fluid balance disorders (Delong and Manning 1994; Aeschbacher 1995; Flecknell 1996). A significant number of rabbits presenting for anaesthesia have been reported to carry *pasteurella multocida* respiratory disease (Flecknell 1996). They have fewer easily accessible veins for venous catheterisation and endotracheal intubation is more technically demanding than in dogs and cats (Wixson 1994; Aeschbacher 1995). Combined with a perceived increased sensitivity to the respiratory depressant effects of anaesthetics and a narrow therapeutic index for many of the anaesthetic agents (Aeschbacher 1995), a higher risk of anaesthetic death could be anticipated. There are no other large-scale studies of anaesthetic death risks to compare to, hence it is difficult to say if there has been improvement in the anaesthesia of rabbits over the last twenty years. However, it is clear there is scope for substantial reductions in mortality. Chapter 5 will investigate major risk factors for anaesthetic death in rabbits to aid identification of modifiable factors and reduce risk.

Mortality risks in other small animal species were generally higher again than those reported in rabbits. Only overall anaesthetic-related mortality risks were calculated, as no data on the denominator health status of the patients anaesthetised were available to allow estimates of ASA stratum-specific risks. Birds appeared to be at particular risk as were small mammals such as hamsters, chinchillas and mice. It is likely that small body size contributes to these high risks, with all these species having high surface area to volume ratios, again predisposing to hypothermia during anaesthesia (Flecknell 1996). Additionally, they generally have high metabolic rates and would be prone to

perioperative hypoglycaemia until they resumed eating postoperatively (Flecknell 1996). Due to their small size, they were less commonly endotracheally intubated and maintaining a patent airway and adequate ventilation would be more difficult. Only a small number of each species were anaesthetised, and the relative inexperience of veterinary surgeons with anaesthetising these patients was likely to have contributed to the high perioperative mortality risks.

Clinic-based risks, as reported for practice type, were generally similar within species for dogs and cats. The notable exceptions were the risks reported for veterinary institutions, which were at least twice as high as those reported for small animal and mixed practices. This was consistent with previous work in which the risk of anaesthetic-related death in referral centres was much higher than that of practice based centres (Hosgood and Scholl 1998; Gaynor, Dunlop et al. 1999; Hosgood and Scholl 2002; Brodbelt, Hammond et al. 2005). Veterinary institutions generally have a higher risk population to anaesthetise and are undertaking longer and more complicated procedures on these patients. Hence, the risks of 0.31% in dogs and 0.60% in cats found in this study are comparable to international studies from veterinary schools (Gaynor, Dunlop et al. 1999; Brodbelt, Hammond et al. 2005). Risks based on the practice standard when excluding veterinary institutions, were again comparable between RCVS hospitals, BSAVA practices and other veterinary practices, suggesting that standards of anaesthesia were comparable across classifications. These risks however were unadjusted for other factors, and clinic level risks will be evaluated further within the multivariable model of risk factors in dogs and cats (Chapters 6 and 7).

Given that the data were collected prospectively within a large-scale multi-centre cohort, it is likely the overall risks reported for dogs, cats and rabbits were representative of the population studied. The health-status stratum-specific risks reported for dogs, cats and rabbits could only be estimated. Based the proportion of each health status group in the control population derived from the case-control study, these estimates were dependent on accurate reflection of the control population by the controls selected. The ASA 3-5 risks were inherently less precise than the ASA 1-2 risks, as a small error in the proportion of controls estimated would have had a large effect on the relatively small denominator of sick patients anaesthetised. In contrast, the low risks for the ASA 1-2 group would be only minimally affected by errors in the

estimates of the proportion of healthy patients being anaesthetised, as the denominator would be little affected by small errors in the proportion of healthy controls. Further, in both dog and cat case-control studies (Chapters 6 and 7), approximately 500 controls were randomly selected for both species, representing approximately 0.5% and 0.7% of the anaesthetised population for the dogs and cats. Hence assuming an unbiased selection of the controls, these estimates are likely to be reasonably reflective of the populations anaesthetised.

The ASA specific risks in rabbits were more preliminary in nature, as these were based on 59 controls and were not randomly selected from the study population, but matched to the cases by clinic and proximity of time (Chapter 5). Hence these risks should be interpreted with caution. The risks for other small animals were also estimates only, due to the relatively small sizes and large confidence intervals. Nonetheless the estimates remain invaluable as there is no other data available for these species.

It is interesting to observe the large proportion of dogs, cats and rabbits that died postoperatively, representing 50-60% of patients. This is in contrast to previous work in which nearer 40% of dogs and cats died postoperatively (Clarke and Hall 1990) and highlights the importance of the postoperative period as a risk period perioperatively. Further that nearly 50% of these postoperative deaths occurred within 3 hours of termination of anaesthesia, this suggests that if closer monitoring and management of patients in this early postoperative period were instituted, then risks could be reduced. That many causes of death were documented as primarily cardiovascular or of respiratory origin was not surprising, given the importance of these two systems to patient homeostasis. The large percentage of unknown cause is of interest however. The lack of definite cause reflects the level of monitoring used during and after anaesthesia, such that precise precipitating events may not be detected and patients are not observed continuously postoperatively. Further the lack of post-mortem evidence (<10% of patients had a post-mortem), also would preclude the classification of death in some cases. The greater percent of unknown cause in rabbits would reiterate the above comments and suggest monitoring of this species might be even less comprehensive than in dogs and cats.

In conclusion, the risks of anaesthetic-related death appear to have decreased in dogs and cats over the last twenty years in the UK and are comparable to other risks

reported internationally. Sick patients remain particularly at risk of perioperative death and should be targeted for improvements in anaesthetic management. Cats, rabbits and other small animal species appear at greater risk of anaesthetic-related death than dogs and particular attention to these species could reduce mortality substantially. The postoperative period was particularly high risk and patient monitoring and management during this period should be targeted to reduce risk.

Chapter 5: Risk Factors for Anaesthetic-Related Death in Rabbits

5.1 Introduction

The risks associated with anaesthetic mortality have been poorly documented in rabbits (Chapter 1). The risk of anaesthetic-related death was much greater in rabbits compared to dogs and cats in the current study (Chapter 4). Identifying major risk factors associated with anaesthetic-related death and improving anaesthetic management of this species could reduce the risk of death significantly. Hence, the aim of this part of the study was to identify risk factors associated with anaesthetic-related death in rabbits.

5.2 Materials and Methods

Nested within the cohort study (see Chapter 2), a matched case-control study was undertaken to identify risk factors associated with anaesthetic-related death for rabbits anaesthetised between the 1st of January 2003 and the 31st December 2003. A case was defined as a perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death was due solely to inoperable surgical or pre-existing medical conditions. A death was considered a case if anaesthesia could not be reasonably excluded as a contributory factor.

Controls were matched by clinic and proximity of time to the case at a 1:1 case - control ratio. The most recent non-death ('control') at the same centre, prior to the case, was identified from the CEPSAF diary by the primary investigator and a CEPSAF case-control questionnaire was requested. If no non-deaths were recorded on the CEPSAF diary in the preceding two months then the most recent non-death subsequent to the case was selected at that centre. Rabbits that died or were euthanased within 48 hours of anaesthesia or sedation were excluded from being considered as controls.

A priori hypotheses for major risk factors were identified. Based on work in other domestic animals it was hypothesised increasing age, poor patient health status, the use of alpha$_2$ adrenoceptor agonists, mask induction, increasing operation time, increasing procedural complexity and dorsal recumbency would be associated with increased risk of anaesthetic-related death (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Johnston, Eastment et al. 2002). Further, it was hypothesised that

the use of isoflurane, the presence of a separate person monitoring the anaesthetic (relative to the person undertaking the procedure), and increasing personnel anaesthetic expertise would be associated with reduced risk of anaesthetic-related death.

Descriptive statistics were recorded for common characteristics of the controls. Univariable analysis of the data was undertaken to determine the association of each variable with the odds of anaesthetic-related death. Intended duration was calculated for intraoperative deaths when no procedure was performed, based on the duration of the same procedure category as described in Table 5.4. For categorical data, maximum likelihood estimates of odds ratios and their 95% confidence intervals, conditional on the number of discordant pairs, were calculated (Breslow and Day 1980; Schlesselman 1982; Hosmer and Lemeshow 2000). McNemar's chi-squared test was applied to test the statistical significance of the association. An exact test based on the binomial distribution was applied when appropriate (Breslow and Day 1980; Kirkwood 1988). For continuous variables, the paired Student's t test or Wilcoxon Signed Rank test, were applied depending on the distributional characteristics (Kirkwood 1988). Biologically important factors and variables significant at the 20% level were retained for evaluation in the multivariable model. Conditional logistic regression was then used and the contribution of these explanatory variables to the model was assessed (Hosmer and Lemeshow 2000). Statistically significant variables ($p<0.05$), based on the likelihood ratio test statistic, were retained in the conditional logistic regression model using a forward stepwise selection approach (Dohoo, Martin et al. 2003). The likelihood ratio test statistic was elected over the Wald test statistic due to its reported more consistent performance particularly with small sample sizes (Hauck and Donner 1977; Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003). Linearity of continuous variables was assessed by categorising variables into quartiles and quintiles and evaluating the effect on odds for incremental increases in the variable (Dohoo, Martin et al. 2003). Interactions of potential biological importance, of the statistically significant main effects, were assessed in the final model (Hosmer and Lemeshow 2000). To explore the model further, an unconditional logistic regression was applied with the pairing variable retained as a random effect, and residual diagnostics and the Hosmer-Lemeshow goodness-of –fit test were used to crudely evaluate the model fit (Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003).

5.3 Results

Eighty-eight anaesthetic-related deaths were recorded during 2003. Of these, 70 (80%) case-control questionnaires were returned during the data collection period of this case-control study and matched controls were requested from the same clinic. Sixty control forms (86% of controls requested) were returned, and one was excluded due to insufficient information being recorded on the case-control questionnaire. This resulted in 59 pairs of cases and controls being taken forward for the case-control analysis. Thirty-five of 117 clinics were represented in this case-control study.

5.3.1 Descriptive Data for Rabbits

Five percent of the cases died on induction of anaesthesia, 31% during maintenance and 64% died postoperatively, of which 50% of the postoperative deaths occurred within 3 hours of anaesthesia (Table 5.1). The primary cause of the anaesthetic-related deaths was classified as cardio-respiratory causes in 35% of the cases, neurological causes in 2% and of unknown origin in 63% (Table 5.2). Of the cardiopulmonary deaths, 10% occurred on induction, 48% occurred during anaesthesia, and 42% postoperatively, whilst 75% of unknown causes occurred postoperatively and 25% on induction or during anaesthesia (Table 5.2).

Table 5.1 Timing of death of the Rabbits

Timing of Death	**Number of Cases**
Induction of anaesthesia	3 (5%)
Maintenance of anaesthesia	18 (31%)
Postoperative death*	38 (64%)
0-3 hours postoperative	19 (50% of postoperative deaths)
3-6 hours postoperative	4 (11% of postoperative deaths)
6-12 hours postoperative	6 (15% of postoperative deaths)
12-24 hours postoperative	5 (13% of postoperative deaths)
24-48 hours postoperative	4 (11% of postoperative deaths)
Total	59

*Postoperative deaths were additionally categorised by time after anaesthesia.

Table 5.2 Primary cause and timing of death in Rabbits

	Timing of Death			
Cause of Death	**Induction**	**Maintenance**	**Postoperatively**	**Total***
Neurological cause	0	0	1	1 (2%)
Cardio-Respiratory cause	2	10	9	21 (35%)
Unknown	1	8	28	37 (63%)
Total	3	18	38	59

*Number of animals and percent of total.

A number of breeds were represented in the cases and controls, including Rex, Dutch breed and various Lops (Table 5.3). The rabbits presented for various procedures, with dental surgery and castration being the most common operations, followed by ovariohysterectomy, minor procedures (e.g. dematting, abscess lancing, and radiography) and least commonly, other major procedures (e.g. bladder stone removal) (Table 5.4). There was a tendency for the cases to present for more complex procedures.

Table 5.3 Rabbit Breeds

Variable	**Cases***	**Controls***
Rex	1 (2%)	2 (3%)
Dwarf	4 (7%)	7 (12%)
Lop	9 (15%)	16 (27%)
Lionhead	2 (3%)	0
Dutch	7 (12%)	4 (7%)
English	3 (5%)	0
Other	33 (56%)	30 (51%)
Total	59 (100%)	59 (100%)

*Number of animals and percent of total.

Table 5.4 Intended procedures in Rabbits.

Variable	Cases*	Controls*
Dental Treatment	30 (51%)	32 (54%)
Castration	7 (12%)	14 (24%)
Other Minor Procedures	7 (12%)	7 (12%)
Spay	3 (5%)	5 (8%)
Other Major Procedures	12 (20%)	1 (2%)
Total	59	59

*Number of animals and percent of total.

Medetomidine and ketamine were most commonly used for induction of anaesthesia (59% of controls, Table 5.5). Hypnorm accounted for approximately 30% of anaesthetic inductions, xylazine and ketamine for 5% and the remainder included mask inductions, propofol, and midazolam and ketamine combinations. About half of the rabbits were maintained with inhalational anaesthesia, of which more than 90% were maintained with isoflurane. Endotracheal intubation was performed in less than 30% of the rabbits, and 34% received some form of fluid support perioperatively (Table 5.6). Most rabbits had a separate person monitoring the anaesthetic. Monitoring of respiratory rate and pulse rate were commonly performed, however other monitoring was less commonly undertaken (Table 5.6).

Table 5.5 Anaesthetic drugs used in Rabbits

Variable	Cases*	Controls*
Hypnorm Anaesthesia	19 (32%)	17 (29%)
Medetomidine and Ketamine Induction	35 (59%)	35 (59%)
Xylazine and Ketamine Induction	3 (5%)	3 (5%)
Endotracheal Intubation	17 (29%)	14 (23%)
Isoflurane maintenance	30 (51%)	27 (46%)
Halothane maintenance	1 (2%)	3 (5%)
Total	59	59

*Number of animals and percent of total.

Table 5.6 Patient management in Rabbits

Variable	Cases*	Controls*
Perioperative fluid therapy	27 (46%)	20 (34%)
Separate person monitoring the anaesthetic	56 (95%)	57 (97%)
Pulse rate monitored	44 (75%)	42 (71%)
Respiratory rate monitored	57 (97%)	56 (96%)
Pulse Oximeter used	21 (36%)	16 (27%)
Recovery continuously monitored	13 (34%) **	16 (27%)
Recovery intermittently monitored (every 5- 15 minutes)	18 (47%) **	41 (70%)
Recovery not monitored / not known	7 (19%) **	1 (3%)
Total	59	59

* Number of patients and percent of total number of cases or controls. ** Postoperative deaths only (38 cases).

5.3.2 Univariable Analysis

The unadjusted associations between risk factors and the risk of anaesthetic-related death, expressed as the conditional odds ratios (Table 5.7a-c), identified increasing patient risk status, increasing urgency of the procedure, longer intended anaesthetic duration, later induction times, and longer procedures with increased odds of anaesthetic-related death. Administration of carprofen was associated with reduced odds. This association was not significant tendency (p=0.10) when only postoperative cases were considered (Table 5.7b).

There were no significant differences in the odds of an anaesthetic-related death associated with the main recumbency of the patient, or the induction and maintenance anaesthetic agents used. There were insufficient discordant pairs to assess the odds associated with the monitoring person and the anaesthetist's postgraduate qualifications. Additionally, comparing deaths occurring during versus after anaesthesia, there were similar numbers of patients receiving the two most common anaesthetic induction combinations, Hypnorm and medetomidine with ketamine. Of the Hypnorm cases, 9 (48%) died during and 10 postoperatively (52%) compared to 11 (31%) during and 24 (69%) postoperatively of the medetomidine and ketamine cases.

Table 5.7.a The association of patient and procedural variables with anaesthetic-related death in Rabbits

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Age in Years Mean (sd)		3.3 (2.0)	3.2 (2.1)			0.77
Sex	Male	34	38	1		
	Female	24	20	1.6	0.7 – 3.6	0.30
	Unknown	1	1			
Neutered	Entire	41	42	1		
	Neutered	12	9	1.3	0.5 – 3.5	0.62
	Unknown	6	8			
Weight in Kg Mean (sd)		2.4 (1.0)	2.3 (0.7)			0.33
Overweight	Not overweight	50	50	1		
	Overweight	4	3	1.3	0.3 – 6.0	0.70
	Unknown	5	6			
ASA grade	ASA 1-2	37	55	1		
	ASA 3-5	22	4	10.0	2.3 – 42.8	<0.001
Urgency	Scheduled	26	41	1		
	Emergency / Urgent	33	18	3.5	1.4 – 8.7	0.004
Intended Procedure	Minor	44	53	1		
	Major	15	6	4.0	1.2 – 14.2	0.02
Procedure Difficulty	Simple	22	32	1		
	Difficult / Moderate	29	27	2.4	0.8 – 6.8	0.09
	No Procedure	8	0			
Recumbency	Dorsal	17	20	1		
	Lateral	8	5	5.0	0.6 – 42.8	0.10
	Sternal	21	28	0.5	0.2 – 1.5	0.20
	Multiple	13	6	5.0	0.6 – 42.8	0.11
Induction Time	9 am - 12 pm	38	47	1		
	12 pm - 9 pm	21	11	3.5	1.2 – 10.6	0.02
	Unknown	0	1			
Duration in minutes Mean (sd)		40.3 (35.0)	32.0 (18.4)			0.11
Duration Intended**	0 – 29 min	13	23	1		
	30 - max	46	36	3.0	1.1 – 8.3	0.03

* Odds ratios (OR) and 95% confidence intervals (CI). Numbers in cases and controls represent the number of patients in each category. ** Duration of anaesthesia for cases that died during anaesthesia is based on the duration of similar procedures in the control population.

Table 5.7.b The association of anaesthetic agent with anaesthetic-related death in Rabbits

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
General anaesthesia or sedation	General anaesthesia	53	51	1		
	Sedation	6	8	0.7	0.2 – 2.3	0.56
Medetomidine (Med) and Ketamine (Ket)	No Med / Ket	24	24	1		
	Med / Ket	35	35	1.0	0.4 – 2.7	1.0
Hypnorm	No Hypnorm	40	42	1		
	Hypnorm	19	17	1.4	0.4 – 4.4	0.56
Induction combination	Med / Ket	35	35	1		
	Hypnorm	19	17	1.0	0.3 – 3.5	1.0
	Other	5	7	1.0	0.2 – 5.0	1.0
Medetomidine Dose	0 - 0.25 mg/kg	24	24	1		
	0.25- max	10	10	2.0	0.4 – 10.9	0.42
	Unknown	1	1			
Ketamine Dose	0 – 15 mg/kg	16	19	1		0.20
	15 – 20	10	11	2.0	0.4 – 10.9	0.67
	20 – max	10	7	3.0	0.3 – 28.8	0.32
	trend			1.9	0.9 – 4.3	0.10
Hypnorm Dose	0 - 2 ml/kg	8	7	1		
	2 – max	10	9	0.3	0.03 – 3.2	0.32
	Unknown	1	1			
Carprofen	No Carprofen	42	30	1		
	Carprofen	17	29	0.2	0.1 – 0.7	0.005
Carprofen2**	No Carprofen	24	30	1		
	Carprofen	14	29	0.3	0.1 – 1.4	0.10
	Intraoperative death	21	0			
Inhalation Agent	None	28	29	1		
	Inhalation agent	31	30	1.1	0.5 – 2.3	0.85

* Odds ratios (OR) and 95% confidence intervals (CI). Numbers in cases and controls represent the number of patients in each category. **Includes only pairs where the case died postoperatively.

Table 5.7.c The association of anaesthetic management with anaesthetic-related death in Rabbits

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Mask Induction	No mask induction	11	7	1		
	Mask induction	20	23	1.0	0.2 – 5.0	1.00
	Injectable anaesthesia	28	29			
Endotracheal Intubation (ET)	No ET intubation	42	44	1		
	ET intubation	17	14	1.4	0.5 – 3.8	0.47
	Unknown	0	1			
Oxygen	No Oxygen	11	14	1		
	Oxygen	48	44	2.3	0.6 – 9.0	0.21
	Unknown	0	1			
Perioperative fluids	No fluids	32	37	1		
	fluids	27	20	1.8	0.7 – 4.2	0.21
	Unknown	0	2			
Record of Anaesthesia	No record	46	50	1		
	Record	13	7	2.3	0.1 – 7.3	0.17
	Unknown	0	2			
Other duties of monitor	No other duties	43	42	1		0.45
	Assisting the op	13	15	0.8	0.3 – 2.0	0.64
	Performing the op	3	2	--	--	--
Pulse oximeter used	No Pulseox	38	43	1		
	Pulseox	21	16	1.8	0.7 – 5.0	0.22
Recovery Quality	Good	11	37	1		
	Poor or moderate	16	16	2.3	0.7 – 7.3	0.17
	Unknown	11	6			
	Intraoperative death	21	0			
Recovery Location	Kennel	21	38	1		
	Not Kennel	13	21	3.0	0.6 – 14.9	0.16
	Unknown	4	0			
	Intraoperative death	21	0			
Surgeon Familiarity with Anaesthetic used	Unfamiliar / familiar	14	9	1		
	Very familiar	43	49	0.4	0.1 – 1.1	0.07
	Unknown	2	1			
Surgeon Postgraduate Qualifications	None	52	48	1		
	Post Qualification	7	11	0.3	0.1 – 1.7	0.16
Anaesthetist Familiarity with anaesthetic used	Unfamiliar / familiar	21	15	1		
	Very familiar	32	38	0.5	0.2 –1.3	0.18
	Unknown	6	6			

* Odds ratios (OR) and 95% confidence intervals (CI). Numbers in cases and controls represent the number of patients in each category.

5.3.3 Multivariable Analysis

Seventeen variables were taken forward to the multivariable level due to being below the screening significance level ($p<0.20$). They included health status (ASA grade), urgency, major versus minor intended procedure, procedure difficulty, patient recumbency, induction time, duration and intended duration, ketamine dose, receiving carprofen (for postoperative deaths and pair only), having a record of anaesthesia, recovery quality, recovery location, veterinarian familiarity with the anaesthetic, veterinarian postgraduate qualification, anaesthetist familiarity with the anaesthetic. Eleven independent variables were retained for multivariable analysis due to their potential biological significance, they included age, sex, the induction combinations used (3 variable), having an inhalation agent, mask induction, receiving oxygen, perioperative fluids, other duties of monitoring person, and using a pulse oximeter. After adjusting for other variables, four factors were retained in the model: health status, intended duration, intended procedure and veterinary surgeon familiarity with the anaesthetic used (Table 5.8).

Table 5.8 The conditional logistic regression model for anaesthetic-related death in Rabbits

Variable	**Categories**	**β**	**s.e. β**	**OR**	**95% CI**	**LRT P value**
ASA grade	ASA 1-2			1		
	ASA 3-5	3.29	1.09	26.9	3.2 – 227.4	< 0.001
Intended Duration of Anaesthesia*	0-29 minutes			1		
	30-max	1.60	0.74	5.0	1.2 – 21.1	0.01
Intended Procedure	Minor			1		
	Major	2.08	0.93	8.0	1.3 – 49.8	0.01
Surgeon Familiarity with Anaesthetic used	Unfamiliar / familiar			1		
	Very familiar	-1.29	0.74	0.3	0.1 – 1.2	0.07

* Duration of anaesthesia for cases that died during anaesthesia is based on the duration of similar procedures in the control population. 112 observations of 118.

Patient health status (ASA grade) was an important risk factor (OR = 26.9, Table 5.8) and confounder of other variables based on its effect on other variables estimates, and was the major independent variable around which the model was built. After adjusting for health status, the intended duration was associated with a 5-fold increase in odds for procedures over 30 minutes. Intended procedure was retained as the third variable and major procedures were associated with odds ratio of 8.0. The final variable associated with outcome was veterinarian familiarity with the anaesthetic used (OR= 0.3), and though its likelihood ratio test p value was just outside the 5% level (p=0.065), it was retained on biological grounds.

The use of pulse oximetry was an alternative to veterinarian's familiarity with the drugs used, as the fourth variable in the model (LRT P = 0.04). However, patients using pulse oximetry were associated with a 4.6 increase in odds (95% CI 0.9 – 22.8) and based on the similar significance and comparable model fit (see below), the veterinarian familiarity with the anaesthetic was considered more biologically plausible even though it had a marginally greater p value (P=0.065). The use of carprofen was also associated with reduced odds, although when considering deaths occurring other than on induction of anaesthesia or only postoperative deaths, this association was no longer significant, and hence this variable was not retained. No further variables were significant variables at the 5% level after adjusting for the four variables. No significant interactions were detected amongst the explanatory variables.

The unconditional logistic regression was undertaken to attempt to evaluate model fit. The odds ratios for ASA grade were 11.1 (95% CI 3.2 – 38.2), intended duration 2.6 (95% CI 1.0 – 7.1), intended procedure 2.3 (95% CI 0.7 – 7.3), and veterinarian familiarity with the anaesthetic 0.5 (95% CI 0.2 – 1.5). Using clinic as the random effect did not improve this model (rho<0.001, LRT p = 1.0). However the model fit was good based on the Hosmer-Lemeshow goodness-of-fit test (p = 0.56), and the delta deviance residual diagnostic statistic (no covariate patterns being greater than 6.0 and only 7 greater than 5.0) (Hosmer and Lemeshow 2000). There were a number of influential covariate patterns, with just over half of patients (n=61 of 118) having delta betas greater than 1.0. However, these were considered biologically plausible and reflected the limited number of covariate patterns based on 4 dichotomous variables (i.e. 16 permutations) (Hosmer and Lemeshow 2000). Model fit was slightly better when

pulse oximetry was used as the fourth variable (Hosmer-Lemeshow goodness-of-fit p = 0.81, delta deviance statistic no patterns greater than 4.0, delta beta statistic 36 covariates greater then 1.0), but on biological grounds veterinarian's familiarity was preferred and retained in the conditional logistic regression model.

Hence in summary, in the final multivariable conditional logistic regression model, higher risk patients (ASA 3-5) were associated with a near 27-fold increased odds of death compared to low risk patients, procedures lasting 30 or more minutes versus less than 30 minutes were associated with a 5.0 fold increase in odds, major versus minor procedures were associated with a 8.0 times increase in odds and the veterinary surgeon being very familiar with the anaesthetic used was associated with a 0.3 odds ratio, compared to their subjective assessment of being familiar or unfamiliar (Table 5.8).

5.4 Discussion

This study has identified a number of factors associated with anaesthetic-related death in rabbits. However it is important to interpret the results in lights of the limitations of the method.

5.4.1 Methodological Considerations

5.4.1.1 Design and Conduct

Case definition and selection were important considerations in evaluating the limitations of the study (Hennekens and Buring 1987) and were discussed in Chapter 2. The definition of anaesthetic-related death was potentially open to inconsistent interpretation by participating centres. Due to this concern, centres were required to return a case-control questionnaire for all perioperative deaths within 48 hours of anaesthesia unless there was clear evidence of no role of anaesthesia. In relation to rabbits the primary investigator then classified all potential cases against the criteria list (Appendix 2.4) to increase consistency of classification and reduce misclassification.

The use of a matched case-control study presented some advantages and disadvantages. The efficiency of undertaking the study was increased by matching the controls by clinic and proximity in time to the cases. Matching for commonly identified confounders, removes this confounder and can increase the statistical power of the

study (Breslow and Day 1980; Hennekens and Buring 1987; Hosmer and Lemeshow 2000). However by their nature, matched studies preclude the evaluation of the matched variable or covariates associated with it (Breslow and Day 1980; Hennekens and Buring 1987; Hosmer and Lemeshow 2000). Though the primary matched variable, clinic identification, was not of specific interest, the commonly used induction drugs appeared closely correlated with the clinic identification, making it difficult to interpret the risks associated with these drugs (see below). Further the potential for seasonal effects on anaesthetic-related death could not be examined due to the matching by time of patient. Matching in the design requires taking account of matching in the analysis using the appropriate regression method, conditional logistic regression (Breslow and Day 1980; Hosmer and Lemeshow 2000). This can effectively reduce the sample size, as it only takes account of those pairs in which the case and control have different exposure histories (i.e. the discordant pairs) (Breslow and Day 1980; Hennekens and Buring 1987; Hosmer and Lemeshow 2000). Hence, the matched approach facilitated the administration of the study, but reduced the power of the study to evaluate anaesthetic agent related effects.

The controls should represent the population of individuals that would have been identified and classified as cases had they developed the outcome (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). The matching process ensured patients contemporary to the cases were selected, and it was likely these would be representative of the underlying population of patients anaesthetised at participating centres. Alternatively, randomising the controls across the cohort of rabbits could have been undertaken, but for efficiency of study administration this was not done. Selection bias, with differential selection of controls on the basis of their exposure histories, was also a potential concern (Hennekens and Buring 1987). However, the matching process was unlikely to encourage selection bias on the basis of the patient exposure histories as the exposure histories would not influence selection other than for the matching variables centre identity and date of procedure, and individual centres could not influence patient selection. The issue of non-response was a further consideration in the rabbit study. The 80% response rate for the cases and the 86% response rate for the controls were considered good based on a suggested aim of a non-response rate of less than 20 to 30% (Dohoo, Martin et al. 2003). Further, the comparable response rates in cases and

controls, have been suggested to support the likelihood that no major bias occurred due to non-response (Dohoo, Martin et al. 2003).

Information or observation bias, particularly errors of misclassification, was a further potential concern (Breslow and Day 1980; Dohoo, Martin et al. 2003). Misclassification of exposure histories by the participating centres was minimised by checking the case-control questionnaires against anaesthetic record forms when available, and by assessing the plausibility of the data. Misclassification of outcome was reduced by checking the patient details to the cohort to ensure the outcomes agreed. Data entry errors were minimised by checking the data twice and randomly checking 20% of the entered data again. There was the potential for recall bias and differential misclassification, with cases being generally completed soon after their death and having more accurate exposure histories than controls (90% of cases returned compared to 25% of controls within 3 months of the anaesthetic). However, the majority of the information required for the forms would be recorded in the practices' patient records, particularly for the main factors of interest. Hence, in general major differential misclassification should have been limited and if errors were made primarily they would have been non-differential in general, and at worst reduce the power of the study and result in associations that tended to unity (Dohoo, Martin et al. 2003).

5.4.1.2 Analysis

Matched sampling requires matched analysis and the conditional logistic regression approach is appropriate (Breslow and Day 1980; Hosmer and Lemeshow 2000). Hosmer and Lemeshow (2000) warn against breaking the matching and analysing with unconditional logistic regression even when the sample size is large, and state that the analysis should be based on the stratum specific conditional likelihood. Dohoo and colleagues (2003) identified that unconditional analysis of a matched dataset will bias the estimates to unity if the matching were done on variables that are confounders, whereas if the matching were not necessary to avoid confounding bias then the unconditional analysis will be less efficient with wider confidence intervals and hence conditional analysis is preferred and was performed here.

The use of the conditional logistic regression approach limited the ease of assessing model fit (Dohoo, Martin et al. 2003). The Hosmer-Lemeshow goodness-of –fit test

is not appropriate for conditional logistic regression models, as it is based on the m-asymptotic approach (m is the number of subjects with the same covariate patterns, in a matched study m=1)(Hosmer and Lemeshow 2000). Overall goodness-of –fit tests have been proposed but are currently not available in standard software (Hosmer and Lemeshow 2000). Dohoo and colleagues (2003) suggest fitting an unconditional logistic regression model and applying standard residual diagnostics and goodness-of-fit tests to give an approximation to model fit assessment, and this was undertaken here.

5.4.2 Descriptive Data

This study highlighted the particularly high risk of death when anaesthetising rabbits compared to dogs and cats (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Gaynor, Dunlop et al. 1999; Joubert 2000; Brodbelt, Hammond et al. 2005), with the postoperative period being a particularly high-risk period. The classification of the vast majority of anaesthetic-related deaths as of unknown cause is noteworthy and suggests that the monitoring of this species during and after anaesthesia needs to be improved. Most rabbits had a separate person monitoring the anaesthetic during the procedure, and most practices observed respiratory pattern and pulse rate, however additional monitoring was infrequently used, and the ability to detect early signs of physiological disturbance may have been limited. Postoperatively, the rabbits were monitored less frequently than during anaesthesia, which may account for the higher percent of these deaths being classified as of unknown cause. However, the observations that 50 percent of the postoperative deaths occurred within the first 3 hours of termination of anaesthesia and that half of these deaths were classified as due to cardiovascular or respiratory causes, suggests that if this early period were specifically targeted for increased monitoring and management, significant reductions in mortality might be achieved.

The descriptive data from the control rabbits gives an interesting insight into commonly used drugs and anaesthetic management. Generalisations from these data must be made with caution as the control rabbits were matched by clinic and, to a lesser extent, in time to the anaesthetic-deaths, and may not be entirely representative of rabbit anaesthetic practice across the study population. Nonetheless, in the control population of rabbits, medetomidine and ketamine was the main combination used, followed by Hypnorm (fentanyl and fluanisone). This trend is consistent with observations recorded from

practitioners attending CPD meetings (Flecknell 2004), and trends in anaesthesia surveyed across the 117 centres involved in the CEPSAF study (Chapter 3). Medetomidine and ketamine are easily administered intramuscularly or subcutaneously, provide predictable sedation and anaesthesia, and are reversed with the alpha$_2$ antagonist, atipamezole (Flecknell 1996), making them an attractive combination. Interestingly, 90% of the rabbits that received an inhalation agent were given isoflurane, as opposed to halothane. This is similar to trends in other companion animal species involved in this study (Chapters 6 and 7), and in a North American survey (Wagner and Hellyer 2000), suggesting isoflurane is becoming more popular than halothane. Endotracheal intubation was used in 23% of control rabbits and was more common than reported in a North American study (10% of these practitioners routinely intubated rabbits)(Wagner and Hellyer 2000).

5.4.3 Risk Factors in Rabbits

A number of variables were highlighted as potential risk factors in the univariable analysis, but in the final multivariable model only patient health status, duration of anaesthesia (intended duration), major versus minor procedures (intended) and familiarity of the surgeon with the anaesthetic used were retained in the model. That patient health status (ASA grade) was a major factor is supported by other work in small animals (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Brodbelt, Hammond et al. 2005), in horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and in man (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati, Ruzzi et al. 2004). Anaesthetic agents cause cardiopulmonary depression and the presence of pre-existing pathology is likely to predispose to greater anaesthetic-induced physiological disturbance (Hall, Clarke et al. 2001). The conceptual framework described in Chapter 2 (Figure 2.1) would support this association, such that poor health status could convert minor physiological depression due to anaesthesia into a relative anaesthetic overdose. These results are

useful as they help to quantify the risks and have clearly identified patients that need particularly careful perioperative management.

Increasing intended duration of anaesthesia was associated with increased odds, suggesting assessing procedure length prior to anaesthesia would aid evaluation of the likely risks. Adjustment for the anticipated duration of anaesthesia was made for those cases that died prior to having their procedure performed, based on the average duration for similar procedures in the control rabbits. Intraoperative deaths would have shorter procedures than expected and these cases would reduce the association of increased risk with increasing duration. Intended duration as a predictive factor for outcome may in part reflect residual confounding by procedure type, for though intended procedure (major or minor) was also retained in the model, some of the reported effect here could have reflected intended procedure type as well as duration. The overlap between procedure duration and procedure type as risk factors was reflected in the conceptual framework (Figure 2.1). Though intended duration has not been frequently reported, the association of increasing duration and risk of complications has been reported previously in horses (Trim, Adams et al. 1988; Young and Taylor 1990; Young and Taylor 1993; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and man (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002). Prolonged anaesthesia predisposes to hypothermia (Waterman 1981; Dhupa 1995), and given their large surface area to volume ratio, rabbits would be particularly susceptible. Additionally, longer periods of cardiopulmonary depression, if present, were likely to have greater effects than short period insults, by increasing cellular metabolic derangement and damage.

Increasing odds associated with increasing intended operation complexity, characterised by procedures being major or minor in the model, is consistent with work in horses (Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004) and man (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). Intended procedure reflects the risk associated with patients presenting for a given procedure and consequently it represents both aspects relating to the impact of the procedure itself and the patient presenting for that procedure. The procedural aspect was likely to reflect the increasing stress more complex and invasive procedures imposed on patient

physiology. More complex procedures may result in greater fluid and blood loss, exposure of body cavities and a tendency to greater hypothermia. The aspect pertaining to the patient presenting for that procedure, also related to the urgency of the procedure and other factors. These associations were reflected in the conceptual framework.

Interestingly, increasing familiarity of the surgeon with the anaesthetic agents used was associated with reduced odds. Though, just outside the 5% level the variable was retained on biological bases and due to the improved model fit with its inclusion. Johnston and colleagues (1995; 2002) were unable to demonstrate an association with increasing familiarity or experience in horses, but work in man suggested complications were associated with staff inexperience (Buck, Devlin et al. 1988; Campling, Devlin et al. 1992; Campling, Devlin et al. 1993). Personnel experience is likely to reflect the potential for human error, the type of procedure undertaken, and anaesthetic management of the patient. There were also trends for reduced risk with the presence of a postgraduate qualification, suggesting that experience and confidence with the drugs used may be important for reducing risk. That the risk associated with the anaesthetist being familiar with the anaesthetic (OR=0.5, LRT p=0.19) was not retained in the model was likely to reflect the greater number of missing values for this variable (number of observations = 94) and the subsequent reduction in power.

The lack of an association with other patient and procedural variables, significant in the univariable analysis, was likely to reflect a combination of confounding, particularly by health status, and the limited power of this study. The time of induction of anaesthesia only just dropped out of the final model after adjusting for health status in particular, suggesting many of the later procedures were at greater risk due to poorer health status more than the time of day. Nonetheless late operation time has been reported by Johnston and colleagues (2002) in the horse, where procedures undertaken outside the normal working day were associated with greater risk. Later starting times of anaesthesia may reflect emergency procedures, result in less personnel being present preoperatively, longer periods of water or food deprivation, and may increase personnel fatigue. The failure of procedure urgency to be retained in the final model also reflected confounding by patient health status, such that the coefficient for urgency was reduced and not significant after adjusting fro health status. Urgent procedures often tend to poorer health status and much of the association initially seen here resulted from

that. However, increasing procedural urgency has been associated with increased risk in horses and man (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Pedersen, Eliasen et al. 1990; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004) and independent of patient health status it is likely to reflect the ability to stabilise the patient prior to anaesthesia.

It is interesting to note that age did not appear to be a risk factor at the univariable or multivariable level. This is in contrast to work in dogs and horses where increasing age was associated with increased risk (Hosgood and Scholl 1998; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004), and man (Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati, Ruzzi et al. 2004) and may result from species differences in terms of a lack of an association or a smaller effect of increasing age such that it was not detected here due to limited power of the study.

The common anaesthetic combinations used were associated with very similar odds in this study. This may in part reflect similar drug related risks. Though cardiopulmonary depression is reported to be greater with medetomidine and ketamine compared to Hypnorm, the presence of a specific reversal agent for medetomidine allowing faster recoveries could balance this out (Mero, Vainionpaa et al. 1989; Flecknell 1996). The similar timing of death for animals receiving medetomidine and ketamine compared to Hypnorm also supports similar drug associated characteristics. An element of the lack of an association may have been due to matching in the study design. Matching controls to cases by clinic predisposed to matching for anaesthetic agents as many clinics used one anaesthetic protocol in rabbits. Hence, the majority of case-control pairs from individual clinics would have had the same induction agents, and these pairs would not have been included in the analysis (concordant pairs).The odds ratios calculated would result from discordant pairs from the subset of centres which used more than one anaesthetic combination in rabbits. Based on the practice survey

(Chapter 3) and the drugs used in the rabbit pairs in the case-control study, there was evidence of use of both major combinations in 12 of the 35 centres (34%), compared to 19 (54%) using medetomidine and ketamine only and 4 (11%) Hypnorm only. This suggests the ability to assess the odds associated with medetomidine and ketamine versus Hypnorm was limited by the matching process.

Unconditional logistic regression, after breaking of the matching, yielded similar odds ratios for the main anaesthetic agents (medetomidine versus no medetomidine OR = 1.3, 95% CI 0.5 – 3.0; Hypnorm versus no Hypnorm OR= 0.9, 95% CI 0.4 – 2.3), and this would support similarities of drug associated risks. However the matching process, more than the matched analysis would have tended to have reduced differences observed between drugs if they were covariates of the matched variable, and again only those centres that used more than one anaesthetic protocol would alter the odds from unity. Dose-response effects were evaluated though these were not significant in the univariable or multivariable models. Notwithstanding the above limitation in methodology, if the drugs used had been strongly associated with death, some evidence would have been observed in this study even if not retained in the final model: this was not seen.

Reduced odds associated with administration of carprofen (a nonsteroidal anti-inflammatory agent) in the univariable analysis may have resulted from many cases dying before the carprofen could be administered, resulting in reduced odds of death when carprofen was use. Fifty-five percent (16 of 29) of control rabbits received carprofen during anaesthesia and a further 21% (6 of 29) received it postoperatively, hence it is likely that a substantial number of intraoperative deaths and some postoperative deaths would not have received carprofen prior to death, irrespective of the intention to treat. In an attempt to account for this potential bias, a comparison of pairs with only postoperative deaths was undertaken. Though there remained a tendency to reduced odds when carprofen was administered in these postoperative pairs, this was not significant and the variable was not retained in the final model. Though previous work does not suggest a protective effect when carprofen is administered, further work is merited.

In summary, this study has identified the postoperative period to be a particularly high-risk period for rabbits undergoing anaesthesia and sedation. Poor patient health

status, increasing duration of anaesthesia and major procedures were important factors associated with increased odds. Increased familiarity with the anaesthetic used would appear to be more important than the specific drugs used. Further work is required to evaluate the risks associated with specific anaesthetic agents in rabbits.

Chapter 6 Risk Factors for Anaesthetic-Related Death in Dogs

6.1 Introduction

Factors associated with anaesthetic death in Dogs have been evaluated infrequently in the veterinary literature and not for nearly 20 years in the UK (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998) (see Chapter 1 Literature Review). The aims of this part of the Study were to evaluate risk factors associated with anaesthetic-related death in Dogs and in a subpopulation of Sick Dogs (see Chapter 2).

6.2 Materials and Methods

A prospective case-control study was undertaken, nested within the cohort of Dogs anaesthetised and sedated at participating practices during the study period (see Chapter 2). A case was defined as a perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death or euthanasia was due solely to inoperable surgical or pre-existing medical conditions. A death was considered a case if anaesthesia or sedation could not be reasonably excluded as a contributory factor. All deaths from the cohort potentially fitting the case definition were evaluated by the independent review panel and classified against a list of criteria as case or not. Controls for this part of the study were prospectively and randomly selected from the cohort of anaesthetised and sedated Dogs at the participating centres during the Study period at a 1:4 Case: Control ratio for the overall Dog Study (classified as the 'Dog Study').

A sub-population of higher risk dogs was also evaluated (classified as the 'Sick Dog Study'). All cases that were classified as 'Sick' (ASA 3-5, see Appendix 2.1), were included as cases in this section of the study. Controls for this study (Sick controls), were randomly and prospectively selected from the cohort of anaesthetised and sedated sick dogs at the participating centres during the study period at a 1:1 Case: Control ratio.

Univariable analysis of the data was undertaken to determine the association of each variable with the odds of anaesthetic-related death. For categorical data, odds ratios (OR) were calculated and the 95% confidence intervals (95% CI) were calculated

for the risk factors using the standard errors obtained as the square root of the variance of the score statistic (Breslow and Day 1980; Schlesselman 1982; Hosmer and Lemeshow 2000). Chi-squared test or Fisher's Exact test were applied to test the statistical significance of the associations for categorical variables where appropriate (Kirkwood 1988). Additionally, for multiple category variables, the likelihood ratio test P value was calculated for the variable, comparing a logistic regression model with the variable included to that without the variable (Hosmer and Lemeshow 2000). When appropriate for multiple category variables, the odds ratio for a one category increase in odds was calculated (a one degree of freedom test for trend, 'trend')(Hosmer and Lemeshow 2000). For continuous variables, the Student's t test or Mann-Whitney U test, were applied (Kirkwood 1988).

Intended duration of anaesthesia was estimated for cases that died before the procedure was performed, by using the mean duration for controls for the same procedure category as described by procedure performed in a similar manner to that described in rabbits (see Table 6.5c). Intended procedure type was recorded in addition to actual procedure to allow categorisation of those cases that died prior to performing the procedure.

Biologically significant factors and variables significant at the 20% level were retained for evaluation in the mixed effects logistic regression model. Stratification of independent variables by potential confounders (e.g. health status) was performed to explore multivariable associations and effect modification prior to multivariable analysis (Breslow and Day 1980). Logistic regression was then used and the contribution of the explanatory variables to the model was assessed using the log likelihood function (Hosmer and Lemeshow 2000). Variables significant ($p<0.05$) based on the likelihood ratio test statistic, were retained in the logistic regression model using a forward selection approach (Dohoo, Martin et al. 2003). Variables with a large number of missing values were excluded from this approach, except when considered biologically important and then a separate category for missing or unknown values was created (Katz 1999). Biologically plausible first order interactions were assessed in the final multivariable model (Hosmer and Lemeshow 2000). Clustering at the clinic level was adjusted for, by using clinic identity as a random effect (Dohoo, Martin et al. 2003). The fit of the final models was assessed with the Hosmer Lemeshow goodness-of-fit statistic and by evaluating the models' residuals with the delta deviance and delta

beta influence diagnostic statistics based on the observed covariate patterns (Hosmer and Lemeshow 2000).

6.3 Results

One hundred and forty nine deaths within 48 hours of anaesthesia or sedation were classified as cases in dogs. One case was excluded as the centre was withdrawn from the study due to being outside the UK (See Chapter 4), resulting in 148 cases for the case-control Study. Ninety-nine cases (67.0%) were graded ASA 3-5 ('Sick'), and 49 cases were ASA 1-2 (33%, 'healthy'). During the study period 616, controls were requested, 503 were returned (82% response rate) and sixteen were excluded (2 were euthanased within 48 hours of the procedure, 4 were duplicates of other controls, 7 were unavailable until after the analysis was performed, and 3 were submitted by the excluded non-UK centre). This resulted in 487 controls being included in the analysis of the Dog Study (Case: Control ratio 1:3.3). Of the 487 controls, 37 were classified as ASA 3-5 (7.6%) and were also used in the Sick Dog study. An additional 132 Sick controls were requested over the study period, 67 were returned (51% response rate) and 5 were excluded (3 were ASA grade 2 and 2 were from the excluded non-UK centre). A total of 99 controls were compared to 99 cases for the Sick Dog study.

The cohort of dogs anaesthetised and sedated (and not dying or being euthanased within 48 hours) during the study consisted of 11,955 sedations (12%) and 84,300 general anaesthetics (88%), in comparison in the case-control study 36 of 487 controls were sedations (7%), these proportions were significantly different ($P<0.001$). However, the Hauck-Anderson corrected 95% confidence intervals for the difference in proportions of sedated dogs, between the case-control and cohort studies, were -7.5 to -2.6%, which biologically was not a substantial difference (Tu 1997; Christley and Reid 2003). When comparing the dog controls to the non-returned controls (Table 6.1), health status, age and major versus minor procedures were not significantly different and the 95% confidence intervals for the difference in proportions suggested reasonable equivalence between returned and non-returned controls (Christley and Reid 2003). The non-returned controls were statistically more likely to by urgent or emergency procedures (compared to scheduled procedures) and were more likely to be sedations (as opposed to general anaesthetics) than the returned controls, however these trends were not

observed in the cat study (Chapter 7) and were likely to reflect the small sample taken of the non-returned controls.

Table 6.1 Comparison of controls and non-returned controls in Dogs

Risk Factor	Proportion of controls	Proportion of non-returned controls	P value	95% CI* for the difference in proportions
Sedation	36/487 (7.4%)	5/23 (21.7%)	0.013	-5.3 to 34.0%
ASA 3-5	37/387 (7.6%)	2/21 (9.5%)	0.75	-13.7 to 17.5%
Urgent or Emergency	69/485 (14.2%)	9/21 (42.8%)	<0.001	4.2 to 53.0%
Major Procedure	87/487 (17.9%)	3/23 (13.0%)	0.55	-21.6 to 11.9%
Age**	5.7 +/- 4.1 years	6.5 +/- 5.3 years	0.42	-2.8 to 1.1 years

*95% Confidence interval (CI) for the difference in proportion between the Controls and non-returned Controls. ** Mean and standard deviation are reported and the 95% CI for the difference between controls and non-returned controls.

6.3.1 Dog Study

The control population of dogs had a mean age of 5.7 years (4.1 standard deviation (sd), with 49% of controls being male and 51% female. Crossbreeds commonly presented (18%), as did terrier (19%) and gun dog breeds (22%), though few pastoral (6%), utility (6%) or toy dogs were seen (5%)(Table 6.5c). Neutering was the most common procedure performed (28%), followed by diagnostic (20%) and minor soft tissue procedures (Table 6.5c).

Most control dogs (87%) were premedicated prior to anaesthesia (Table 6.2). Acepromazine combinations were most commonly used (78% of controls), 5% had medetomidine combinations prior to anaesthesia, and 4% had benzodiazepine and opioid combinations. Both acepromazine and medetomidine were most often combined with butorphanol or buprenorphine. Anaesthesia was induced with propofol in the majority of dogs, followed by thiopentone and other combinations (Table 6.3). Medetomidine combinations were mostly used for sedation as opposed to anaesthesia (88% of medetomidine inductions were for sedation). Anaesthesia was primarily

maintained with isoflurane (Table 6.4). Those patients that did not receive an inhalation agent were generally only sedated.

Table 6.2 Premedication given to Dogs

Premedication	**Cases***	**Controls***
No Premedication	45 (30%)	62 (13%)
Acepromazine Combinations	64 (43%)	378 (77%)
Medetomidine Combinations	4 (3%)	26 (5%)
Benzodiazepine / Opioid Combinations	35 (24%)	21 (5%)
Total	148 (100%)	487 (100%)

* Number and percent of total (%).

Table 6.3 Induction agents used for anaesthesia and sedation in Dogs

Induction agent	**Cases***	**Controls***
Thiopentone	14 (9%)	120 (25%)
Propofol	112 (76%)	319 (65%)
Medetomidine Combinations	4 (3%)	33 (7%)
Mask Induction	12 (8%)	6 (1%)
Other Methods of Induction	6 (4%)	9 (2%)
Total	148 (100%)	487 (100%)

* Number and percent of total (%).

Table 6.4 Maintenance agents used for anaesthesia and sedation in Dogs

Maintenance agent	Cases*	Controls*
Isoflurane	104 (70%)	396 (81%)
Halothane	19 (13%)	41 (9%)
Sevoflurane	5 (3%)	10 (2%)
Injectable Maintenance only	20 (14%)	40 (8%)
Total	148 (100%)	487 (100%)

* Number and percent of total (%).

Approximately 29% of control dogs had intravenous catheters placed perioperatively and 19% received perioperative intravenous fluids. Intraoperative monitoring was primarily undertaken by a qualified veterinary nurse (85%), with 5% having an unqualified nurse, 8% a separate veterinary surgeon and 2% having no person monitor the patient (Table 6.5g). Forty-four percent had a written record of the anaesthetic. Monitoring was primarily by monitoring patient pulse and respiratory rates (70% and 94% respectively), though pulse oximetry was also commonly used (51% of controls). Additional monitoring methods were infrequently used, with only 10% of controls being monitored with capnography, arterial blood pressure monitoring and electrocardiography (Table 6.5g). Postoperatively, patients were generally observed by a nurse, and generally were checked every five minutes or more (34% continuously monitored, 69% checked every five or more minutes). Postoperative temperature was only taken in 14% of controls.

The procedures were most often undertaken by a junior veterinary surgeon (59% of controls, Table 6.5h), whilst a senior veterinary surgeon undertook 35% of procedures and locum veterinary surgeons 5%. Twenty-three percent (110 controls) of the controls were undertaken by a veterinary surgeon with a non-anaesthesia postgraduate qualification, and 3% (13 controls) with a postgraduate qualification in veterinary anaesthesia (RCVS Certificate / Diploma, European Diploma, PhD). Of 38 controls monitored by a veterinary surgeon, 58% (22 controls) were monitored by a veterinary surgeon with a postgraduate qualification in veterinary anaesthesia, and 8% (3 controls) with a non-anaesthesia postgraduate qualification.

6.3.1.1 Univariable Associations

The mean age of cases was significantly older than controls (8.0 years (4.2 sd) and 5.7 years (4.1sd) respectively, $p<0.001$). Additionally, there were significant trends to increasing odds of anaesthetic-related death for both extremes of age (Table 6.5a). Mean patient weight was not different (21.8 kgs (15.3 sd) and 21.5 kgs (12.9 sd) respectively, $p=0.84$), but low patient weight and estimation of weight were associated with increased odds (Table 6.5a). Cocker Spaniels, German Shepherd Dogs (GSD) and West Highland White Terriers were individual breeds at increased odds compared to cross breeds, and Pastoral, Utility and Toy dogs were breed groups at increased odds (Table 6.5a). Referred patients (not primary) and patients having undergone previous anaesthetics or sedations in the last month were at increased odds (Table 6.5a).

Preoperative disease was markedly associated with increased odds of anaesthetic-related death (Table 6.5b), as was poor patient health status, as described by the ASA health status (Anon 1963). Performing preoperative blood and other tests prior to anaesthesia were associated with increased odds. Preoperative withholding of food and water were associated with reduced odds. Urgency of the procedure untaken, procedure complexity (major versus minor) and procedure difficulty (assessed by the operating veterinary surgeon) were associated with increased odds (Table 6.5c). Procedures undertaken in dorsal or sternal recumbency compared to lateral recumbency tended towards increased odds, whilst those in more than one position tended towards reduced odds. Cases had significantly longer duration of anaesthesia than controls (73.2 min (64.0) and 55.1 min (41.5) respectively, $p<0.001$), and increasing duration of anaesthesia was associated with a tendency to increased odds of death. This association was more clearly seen with the intended duration (82.1 min (58.3) for case and 55.1 min (41.5) for controls, $p<0.001$). Late start times and procedure undertaken during the night and early morning were associated with increased odds.

Compared to not receiving premedication, having acepromazine or medetomidine was associated with reduced odds and benzodiazepines or opioids with increased odds (Table 6.5d). Induction of anaesthesia with propofol and mask inductions were associated with increased odds compared to thiopentone. Halothane anaesthesia and maintenance with injectable anaesthesia were associated with an increased odds

compared to isoflurane (Table 6.5d). Controlled ventilation was associated with increased odds as was perioperative fluid therapy (Table 6.5e).

Monitoring by a veterinary surgeon was associated with increased odds of anaesthetic-related death (Table 6.5f). There was a non-significant tendency to simultaneous performing of the procedure and monitoring the patient being associated with increased odds. Good recovery quality was associated with reduced odds, whilst taking the patient's temperature postoperatively was associated with increased odds (Table 6.5.f). Procedures undertaken by a veterinary surgeon with a postgraduate veterinary qualification and being a veterinary surgeon as the anaesthetist were associated with anaesthetic-related death (Table 6.5f).

Table 6.5.a The association of patient variables with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Categorical						<0.001
Age	0- ≤ 0.5 years	8	23	2.7	1.1– 7.0	0.03
	0.5 – 5 years	25	195	1		
	5 – 12 years	81	227	2.8	1.7 – 4.6	<0.001
	12 years - max	34	42	6.3	3.3 – 12.2	<0.001
Sex	Male	69	238	1		
	Female	79	249	1.1	0.8 – 1.6	0.63
Neutered	Entire	73	274	1		
	Neutered	64	202	1.2	0.8 – 1.7	0.37
	Unknown	11	11			
Categorical						0.01
Weight	0-5 kg	18	22	3.3	1.6 – 7.0	<0.001
	5-15 kg	39	159	1		
	15- max	91	305	1.2	0.8 – 1.9	0.36
	Unknown	0	1			
Overweight	Not overweight	114	384	1		
	Overweight	29	90	1.1	0.8 – 1.7	0.73
	Unknown	5	13			
Scales used	Scales	122	466	1		
	Estimate	26	20	5.0	2.6 – 9.3	<0.001
	Unknown	0	1			
	Adjusted ASA2**			2.8	1.0– 7.8	0.04
Breed						0.05
	Crossbred	17	88	1		
	Cocker spaniel	9	16	2.9	1.1 – 7.8	0.03
	GSD	9	18	2.6	1.0 – 6.8	0.05
	WHWT	6	9	3.5	1.1 – 11.3	0.03
	Hounds	8	30	1.4	0.5 – 5.5	0.50
	Working Dogs	13	50	1.3	0.6 – 3.0	0.47
	Terriers	25	90	1.4	0.7 – 2.9	0.30
	Gun Dogs	21	105	1.0	0.5 – 2.1	0.92
	Pastoral Dogs	13	28	2.4	1.0 – 5.6	0.04
	Utility	15	30	2.6	1.1 – 5.9	0.02
	Toy	12	23	2.7	1.1 – 6.6	0.02
Primary	Primary patient	118	437	1		
Case	Referral patient	30	48	2.3	1.4 – 3.8	<0.001
	Unknown	0	2			
	Adjusted ASA2**			1.3	0.7 – 2.4	0.46
Previous	None	92	402	1		
Anaesthetics	One or more	41	58	3.1	1.9 – 4.9	<0.001
within the month	Unknown	15	27			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column. **Odds ratios are additionally reported adjusted for health status (ASA2) when confounding by health status was observed.

Table 6.5.b The association of further patient variables with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Preoperative disease						<0.001
	None	4	212	1		
	Cardiopulmonary	35	50	37.1	10.4 – 132.4	<0.001
	Neurological	9	14	34.7	7.7 – 150.4	<0.001
	Digestive	61	53	61.0	15.9 – 233.9	<0.001
	Urogenital	14	33	22.5	6.2 – 82.0	<0.001
	Other	24	113	10.6	3.5 – 32.5	<0.001
ASA grade (ASA3)						<0.001
	ASA 1-2	49	450	1		
	ASA 3	37	30	11.3	6.1 – 21.1	<0.001
	ASA 4-5	62	7	81.3	26.8- 247.3	<0.001
	Trend+			9.8	6.7 – 14.2	<0.001
ASA grade (ASA2)	ASA 1-2	49	450	1		
	ASA 3-5	99	37	24.6	13.4 – 45.0	<0.001
Preoperative examination	No	4	18	1		
	Yes	143	469	1.4	0.5 – 4.1	0.57
	Unknown	1	0			
	Adjusted ASA2**			0.5	0.2 – 1.5	0.18
Preoperative bloods	No	62	339	1		
	Yes	84	146	3.1	2.1 – 4.7	<0.001
	Unknown	2	2			
	Adjusted ASA2**			1.5	1.0 – 2.5	0.07
Other tests	No	62	399	1		
	Yes	85	86	6.3	4.1 – 9.8	<0.001
	Unknown	1	2			
	Adjusted ASA2**			1.9	1.2 – 3.1	0.87
Starved Preoperatively	No	11	5	1		
	Yes	120	475	0.1	0.04 – 0.3	<0.001
	Unknown	17	7			
	Adjusted ASA2**			0.9	0.3 – 3.0	0.85
Water withheld	No	65	175	1		
	Yes	63	291	0.6	0.4 – 0.9	0.01
	Unknown	20	20			
	Adjusted ASA2**			0.9	0.6 – 1.5	0.82

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of the 'P Value' column. **Odds ratios are additionally reported adjusted for health status (ASA2) when confounding by health status was observed. +'Trend' represents the odds ratio for a one-category increase in the variable.

Table 6.5.c The association of procedural factors with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Urgency						<0.001
	Scheduled	48	416	1		
	Urgent	58	61	8.2	4.9 – 13.7	<0.001
	Emergency	42	8	45.5	16.8 – 122.9	<0.001
	Unknown	0	2			
	Trend+			7.4	5.2 – 10.4	<0.001
Procedure Performed						<0.001
	Neutering	3	134	1		
	Dental	6	45	6.0	1.4 – 25.6	0.01
	Diagnostics	18	99	8.1	2.2 – 29.5	0.001
	Soft tissue minor	9	120	3.4	0.9 – 12.8	0.06
	Soft tissue major	69	39	79.0	15.4 – 406.5	<0.001
	Orthopaedics	11	45	11.4	2.8 – 46.2	<0.001
	Neurological	4	5	35.7	4.9 – 261.0	<0.001
	No procedure	28	2			
Intended Procedure	Minor	53	400	1		
	Major	95	87	8.2	5.2 – 13.0	<0.001
	Adjusted ASA2**			4.2	2.5 – 7.0	<0.001
Procedure Difficulty						<0.001
	Simple	28	286	1		
	Moderate	55	167	3.4	2.0 – 5.6	<0.001
	Difficult	28	27	10.6	5.1 – 21.8	<0.001
	V difficult	8	4	20.4	5.3 – 78.6	<0.001
	No procedure	27	0			
	Unknown	2	3			
Recumbency						0.01
	Lateral	36	125	1		
	Dorsal	75	185	1.4	0.9 – 2.2	0.14
	Sternal	13	36	1.3	0.6 – 2.6	0.55
	Multiple	24	138	0.6	0.3 – 1.1	0.08
Duration						0.006
	0-29 min	36	103	1		
	30-59 min	37	218	0.5	0.3 – 0.8	0.01
	60-89 min	28	90	0.9	0.5 – 1.6	0.69
	90 – max	46	75	1.8	1.0 – 3.0	0.04
	unknown	1	1			
Duration intended						<0.001
	0-59 min	63	321	1		
	60-119 min	53	121	2.2	1.5 – 3.4	<0.001
	120 –max	30	44	3.6	2.1 – 6.2	<0.001
	unknown	1	1			
	Trend+			1.9	1.5 – 2.5	<0.001
Induction Time						<0.001
	8 am - 12 pm	72	359	1		
	12 pm - 5 pm	56	116	2.4	1.6 – 3.6	<0.001
	5 pm – 8 am	19	8	11.8	4.8 – 29.5	<0.001
	unknown	1	4			
	Trend+			2.9	2.1 – 3.9	<0.001

*Odds ratios (OR) and 95% confidence intervals (CI). **ORs adjusted for health status (ASA2).

Table 6.5.d The association of anaesthetic agents with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
General anaesthesia or sedation	General anaesthetic	140	451	1		
	Sedation	8	36	0.7	0.3 – 1.6	0.40
Premedication+						<0.001
	None	45	62	1		
	Acepromazine	64	378	0.2	0.1 – 0.4	<0.001
	Medetomidine	4	26	0.2	0.1 – 0.7	<0.001
	BZ / Opioids only	35	21	2.3	1.2 – 4.5	0.01
Induction agents						<0.001
	Thiopentone	14	120	1		
	Propofol	112	319	3.0	1.7 – 5.9	<0.001
	Medetomidine	4	33	1.0	0.3 – 3.4	0.95
	Mask induction	12	6	17.1	4.7 – 62.2	<0.001
	Other	6	9	5.7	1.7 – 19.3	0.01
Inhalation Agents						0.05
	Isoflurane	104	396	1		
	Halothane	19	41	1.8	1.0 – 3.2	0.05
	Sevoflurane	5	10	1.9	0.6 – 5.7	0.24
	None	20	40	1.9	1.1 – 3.4	0.03
Induction / Maintenance Combinations						<0.001
	Injectable/Isoflurane	93	389	1		
	Injectable/Halothane	19	41	1.9	1.1 – 3.5	0.03
	Injectable/Sevoflurane	2	8	1.0	0.2 – 5.0	1.0
	Inhalational Only	14	9	6.5	2.7 – 15.8	<0.001
	Injectable Anaesthesia	12	4	12.5	3.8 – 41.3	<0.001
	Injectable Sedation	8	36	0.9	0.4 – 2.1	0.9
Mask Induction	No mask induct	114	437	1		
	Mask induction	14	9	6.0	2.5 – 14.4	<0.001
	Adjusted ASA2**			4.8	1.5 – 15.7	0.01
Endotracheal Intubation (ET)	No ET tube	11	40	1		
	ET tube	137	447	1.1	0.6 – 2.2	0.76
Oxygen	No Oxygen	7	34	1		
	Oxygen	141	445	1.5	0.7 – 3.5	0.34
Nitrous oxide	No nitrous oxide	127	400	1		
	Nitrous oxide	20	83	0.8	0.5 – 1.3	0.30
	Unknown	1	4			

*Odds ratios (OR) and 95% confidence intervals (CI). Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of the 'P Value' column. **ORs adjusted for health status (ASA2). + Includes combinations of premedicant with other drugs.

Table 6.5.e The association of management and monitoring factors with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Ventilation	Spontaneous	116	462	1		
	Controlled	31	22	5.6	3.1 – 10.3	<0.001
	Unknown	1	3			
	Adjusted ASA2**			3.0	1.4 – 6.6	0.003
Perioperative fluids						<0.001
	No fluids	34	345	1		
	IV Catheter only	6	49	1.2	0.5 – 3.1	<0.001
	Fluids given	108	93	11.8	7.0 – 20.0	<0.001
Monitoring person						<0.001
	Vet	33	40	3.2	1.9 – 5.4	<0.001
	Nurse	112	440	1		
	No separate person	3	7	1.7	0.4 – 6.6	0.45
Other duties of monitor						0.71
	No other duties	119	384	1		
	Performing the op	3	7	1.4	0.4 – 5.4	0.6
	Assisting the op	25	95	0.9	0.5 – 1.4	0.5
	Unknown	1	1			
Record	No record	72	268	1		
	Record	71	212	1.3	0.9 – 1.8	0.24
	Unknown	5	7			
Pulse monitored	No pulse	43	145	1		
	pulse	105	342	1.0	0.7– 1.6	0.87
	Adjusted ASA2**			0.7	0.4 – 1.2	0.19
Respiratory rate monitored	No respiratory rate	15	30	1		
	Respiratory rate	133	457	0.6	0.3 – 1.1	0.10
Pulse oximeter used	No Pulse oximeter	68	241	1		
	Pulse oximeter	80	246	1.2	0.8 – 1.7	0.45
Capnography used	No Capnograph	126	438	1		
	Capnograph	22	49	1.6	0.9 – 2.7	0.10
Arterial Blood Pressure						0.66
	None	132	440	1		
	Direct	3	5	2.0	0.5 – 8.5	0.34
	Indirect	13	42	1.0	0.5 – 2.0	0.94
ECG	None	124	432	1		
	ECG	24	55	1.52	0.90 – 2.56	0.11

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category at the top of the 'P Value' column.

**ORs are additionally reported adjusted for health status (ASA2) when confounded by health status.

Table 6.5.f The association of recovery and personnel variables with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Recovery Quality						<0.001
	Good	24	371	1		
	Moderate	19	86	3.4	1.8 – 6.6	<0.001
	Poor	7	4	27.1	6.8 –	<0.001
	Unknown	2	26		108.2	
	No full recovery	96	0			
Recovery observed						0.23
	Continuously	28	191	1		
	Every 5 minutes	15	161	0.6	0.3 – 1.2	0.18
	10 minutes +	20	120	1.2	0.6 – 2.1	0.68
	Unknown	2	15			
	No recovery	83	0			
Rectal Temperature Taken (intraoperative deaths excluded)	No	51	415	1		
	Yes	17	68	2.0	1.1 – 3.7	0.02
	Unknown	1	4			
	Adjusted ASA2**			1.0	0.5 – 2.0	0.95
Veterinary surgeon familiarity with anaesthetic	Very Familiar	125	435	1		
	Familiar or Unfamiliar	15	40	1.3	0.7 – 2.4	0.40
	Unknown	8	9			
Veterinary surgeon type						0.17
	Senior	64	171	1		
	Veterinarian	77	289	0.7	0.5– 1.0	0.08
	Junior	6	27	0.6	0.2 – 1.5	0.27
	Veterinarian Locum	1	0			
	Unknown					
Veterinary surgeon Postgraduate qualifications						<0.001
	None	91	364	1		
	Anaesthesia	7	13	2.2	0.8 – 5.6	0.11
	General	48	110	1.8	1.2 – 2.6	0.01
	Unknown	2	0			
Anaesthetist Familiarity with Anaesthetic	Very familiar	126	386	1		
	Familiar or Unfamiliar	17	70	0.7	0.4 – 1.3	0.31
	Unknown	5	31			
Anaesthetist type						<0.001
	Vet	35	43	1		
	Nurse	79	291	0.33	0.20 –	<0.001
	Unqualified Nurse	34	153	0.27	0.56	<0.001
					0.15 – 0.50	

*Odds ratios (OR) and 95% confidence intervals (CI). Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of the 'P Value' column. **ORs adjusted for health status (ASA2).

6.3.1.2 Multivariable Model

Table 6.6 Final mixed effects logistic regression model of the risk of anaesthetic-related death in Dogs

Variable	Categories	β	s.e. β	OR*	95% CI*	LRT P value
ASA grade	ASA 1-2					<0.001
	ASA 3					
	ASA 4 – 5					
	Trend+	1.80	0.29	6.1	3.4 – 10.8	
Urgency	Scheduled					<0.001
	Urgent					
	Emergency					
	Trend+	0.92	0.27	2.5	1.5 – 4.3	
Intended Procedure	Minor			1		<0.001
	Major	1.65	0.40	5.2	2.4 – 11.5	
Categorical Age	0- ≤ 0.5 years	0.30	0.86	1.3	0.2 – 7.2	<0.001
	0.5 – 5 years					
	5 – 12 years	0.35	0.39	1.4	0.7 – 3.1	
	12 years - max	2.29	0.51	9.8	3.6 – 26.6	
Duration intended (per 10 minute increment)		0.059	0.032	1.06	1.00 – 1.13	0.05
Categorical Weight	0-5 kg	2.03	0.60	7.6	2.4 – 24.7	0.003
	5-15 kg			1		
	15- max	0.15	0.35	1.2	0.6 – 2.3	
Induction and Maintenance Agents						<0.001
	Injectable / Isoflurane			1		
	Injectable / Halothane	1.77	0.53	5.9	2.1 – 16.6	
	Injectable / Sevoflurane	-1.10	1.65	0.3	0.0 – 8.5	
	Inhalational Anaesthesia	1.78	0.82	5.9	1.2 – 29.3	
	Injectable Anaesthesia	4.27	0.88	71.4	12.7 – 402.5	
	Injectable Sedation	0.40	0.64	1.5	0.4 – 5.2	
Intercept		- 16.02	2.08			
Random Effect Clinic identity (Rho)		0.16	0.03			0.05

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with corresponding Likelihood Ratio Test (LRT) P values. +'Trend' represents the odds ratio for a one-category increase in the variable. Number of observations 632 out of 635.

In developing the model, health status as defined by ASA grade was retained in the model due to its low likelihood ratio test p value, its major role as a confounder and its biological importance. Urgency was also retained in the model due to its low likelihood ratio test p value and biological significance. Categorisation of age suggested

increased odds of death with low and increasing age. A similar trend was seen when fitting a fractional polynomial for age, with age to the cube having the lowest P value (Royston, Ambler et al. 1999). The likelihood ratio test static P values were low (<0.001) and the model deviances were similar when categorical, linear or polynomial versions of age were incorporated into the model. Categorical age was preferred over the fractional polynomial and linear versions due to its easier clinical interpretation (Dohoo, Martin et al. 2003).

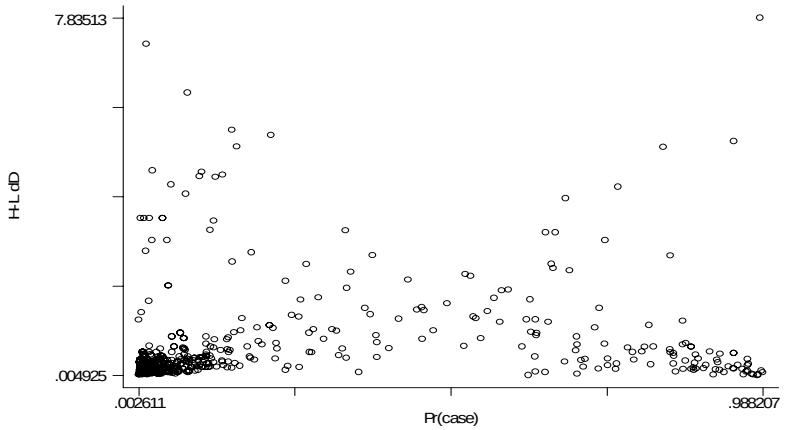
When exploring the association of duration with outcome, the intended duration had lower likelihood ratio test p values than actual duration, due to the effect of intraoperative deaths increasing the odds seen with shorter duration procedures. Categorical intended duration suggested a linear increase in odds with increasing duration and this was supported when fitting a fractional polynomial for intended duration, as the linear model had similar deviance to the polynomial model (Royston, Ambler et al. 1999). The linear version of intended duration was retained over the other versions due to its lower LRT P value. Categorical weight was retained in the model due to its likelihood ratio test p value. The induction and maintenance agent combination was retained as the final variable with the main associations being increased odds with halothane versus isoflurane and total inhalation anaesthesia. No biologically significant interactions were observed between the factors present in the multivariable model.

In the final multivariable model, an increase of one category in poor patient health status (ASA3) was associated with a 6.1 fold increase in odds, an incremental increase in procedural urgency was associated with a 2.5 increase in odds, whilst major versus minor intended procedure was associated with a 5.2 increase in odds. There was a linear increase in odds of 1.06 per a 10 minute increase in intended duration, patients 12 years or older were 9.8 times more likely to die, and patients weighing less than 5 kg were associated with an 7.6 fold increase in odds. Maintenance with halothane and total inhalational anaesthesia were associated with nearly a 6-fold increase in odds compared to isoflurane. Injectable anaesthesia was associated with a 71.4 times increase in odds.

The goodness of fit as assessed by the Hosmer Lemeshow goodness-of-fit statistic was good (P value = 0.81) (Hosmer and Lemeshow 2000). Further evaluation of the model was undertaken with the use of the delta deviance regression residual (Hosmer and

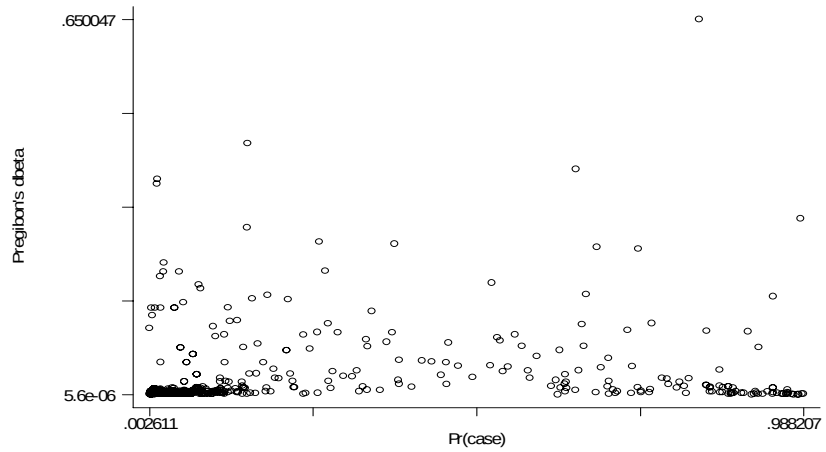
Lemeshow 2000). Only 5 covariate patterns had values over 6 and were identified as particularly poorly fitting of the data, further supporting the good fit of the model (Figure 6.1). Evaluation of the delta beta diagnostic statistic identified only 2 relatively influential covariate patterns with a delta beta greater than 0.5 and none greater than 0.7 (Figure 6.2). These observations were checked for errors and none found. When the model was run without these two covariate patterns the parameter estimates were minimally changed, suggesting minimum influence on the observed coefficients. Hence these covariate patterns were retained in the model. There was evidence of clustering at the clinic level (rho=0.16, standard error 0.03, p=0.053) and clinic identity was retained as the random effect in the model.

Figure 6.1 The Delta Deviance diagnostic statistic versus the estimated probability for the Dog model



*H-L dD, Hosmer-Lemeshow delta deviance diagnostic statistic. Pr(case), probability of being a case. J=437 covariate patterns.

Figure 6.2 The Delta Beta diagnostic statistic versus the estimated probability for the Dog model



*Dbeta, Delta Beta diagnostic statistic. Pr(case), probability of being a case. J=437 covariate patterns.

6.3.2 Sick Dog Study

The mean age of controls in the sick population was 8.9 (sd 3.9), with 47% male and 53% female. Eighteen percent of controls were crossbred, with terrier and gun dog breeds also well represented (Table 6.7a). The majority of dogs were primary cases (80%). Eighty percent were ASA grade 3, 20% ASA grade 4 and the presenting conditions were mostly cardiopulmonary, digestive or urinary disease (Table 6.7b). The majority had had preoperative bloods (77%) and additional tests (72%), and most were starved (89%) (Table 6.7b). In contrast to the general study population, the majority of Sick Dog procedures were urgent or emergency status (60%), more were major procedures compared to minor (59%) and mean duration of procedures was longer (78.7 minutes +/- 59.6sd, Dog study 55.1 minutes +/- 41.5 sd, $p< 0.001$)(Table 6.7c).

Premedication was mostly undertaken with acepromazine combinations (57%), and rarely with medetomidine (2%) (Table 6.7d). Induction of anaesthesia was primarily with propofol (84%) and maintenance with isoflurane (87%, Table 6.7d). Eighty-one percent of dogs had an intravenous catheter placed and 68% received perioperative fluid therapy. More patients were monitored by a veterinary surgeon (21%, Table 6.7f) compared to the general study population, though monitoring remained primarily pulse rate (77%), respiration rate (93%) and pulse oximetry (65%). Further monitoring was only seen in 10 to 20% of the Sick controls, though more Sick patients were

monitored continuously postoperatively (47%) and thirty-one percent had there temperature taken postoperatively. Junior veterinary surgeons undertook the majority of procedures (61%), though 34% of veterinary surgeon had a postgraduate qualification (34%).

6.3.2.1 Univariable Associations

Increased odds of anaesthetic-related death at the univariable level were associated with extremes of weight, estimating patient weight, previous anaesthetics, ASA grade 4 or 5, increasing procedure urgency and difficulty, major versus minor procedures, maintenance other than with isoflurane, controlled ventilation, intravenous fluid therapy, and poor recovery quality (Tables 6.6a-f). Reduced odds were associated with preoperative blood tests, starvation, longer procedure duration, premedication agents used, administration of nitrous oxide and having an unqualified nurse monitor the anaesthetic. Cases were not significantly different from the controls in age (case 8.2+/-3.9 years (mean +/- sd), controls 8.9+/-3.9 years, p=0.19), weight (cases 22.8+/-15.8 kg, controls 21.4+/-12.1 kg, p=0.46) or duration of anaesthesia (cases 71.0+/-67.1 min, controls 78.7+/-59.6, p=0.39).

Table 6.7.a The association of patient variables with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Categorical Age						0.31
	0- ≤ 0.5 years	5	2	3.2	0.5– 21.2	0.21
	0.5 – 5 years	11	14	1		
	5 – 12 years	64	56	1.5	0.6 – 3.5	0.40
	12 years - max	19	27	0.9	0.3 – 2.4	0.83
Sex	Male	44	47	1		
	Female	55	52	1.1	0.6 – 2.0	0.67
Neutered	Entire	48	53	1		
	Neutered	47	45	1.2	0.7 – 2.0	0.62
	Unknown	4	1			
Categorical						0.01
Weight	0-8 kg	20	11	3.7	1.4 – 10.0	0.01
	8-20 kg	18	37	1		
	20- max	61	50	2.5	1.3 – 5.0	0.01
	Unknown	0	1			
Overweight	Not overweight	75	75	1		
	Overweight	20	20	1.0	0.6 – 1.7	1.00
	Unknown	4	4			
Scales used	Scales	75	94	1		
	Estimate	24	5	6.02	2.1 – 17.2	<0.001
Breed						0.26
	Crossbred	10	18	1		
	Cocker spaniel	5	1	9.0	0.8 – 108.4	0.04
	GSD	8	7	2.1	0.6 – 7.6	0.05
	WHWT	4	1	7.2	0.6 – 87.0	0.07
	Hounds	4	9	0.8	0.2 – 3.3	0.76
	Working Dogs	7	6	2.1	0.5 – 8.3	0.27
	Terriers	13	17	1.4	0.5 – 4.0	0.56
	Gun Dogs	17	19	1.6	0.6 – 4.5	0.36
	Pastoral Dogs	12	7	3.1	0.9 – 11.0	0.07
	Utility	10	6	3.0	0.8 – 11.4	0.09
	Toy	9	8	2.0	0.6 – 7.1	0.26
Primary Case	Primary patient	75	79	1		
	Referral patient	24	19	1.3	0.7 – 2.6	0.41
	Unknown	0	1			
Previous Anaesthetics	None	60	78	1		
or Sedations	One or more	30	14	1.7	1.1 – 2.6	0.025
	Unknown	9	7			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column.

Table 6.7.b The association of further patient variables with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Preoperative disease						0.06
	Cardiopulmonary	26	32	1		
	Neurological	6	4	1.9	0.5 – 7.4	0.38
	Digestive	50	32	1.9	1.0– 3.9	0.06
	Urogenital	9	18	0.6	0.2 – 1.6	0.32
	Other	8	13	0.8	0.3 – 2.1	0.59
ASA Grade	ASA3	37	79	1		
	ASA4-5	62	20	6.6	3.3 – 13.4	<0.001
Preoperative examination	No	0	0			
	Yes	98	99			
	Unknown	1	0			
Preoperative bloods	No	38	23	1		
	Yes	61	76	0.5	0.3 – 0.9	0.02
Other tests	No	31	27	1		
	Yes	67	71	0.8	0.4 – 1.5	0.53
	Unknown	1	1			
Starved Preoperatively	No	11	4	1		
	Yes	73	88	0.3	0.1 – 1.0	0.04
	Unknown	15	7			
Water withheld	No	44	53	1		
	Yes	36	34	1.3	0.7 – 2.4	0.44
	Unknown	19	12			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column.

Table 6.7.c The association of procedural factors with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Urgency						<0.001
	Scheduled	16	40	1		
	Urgent	44	48	2.3	1.1 – 4.7	0.02
	Emergency	39	11	8.9	3.2 – 24.7	<0.001
	Trend+			2.9	1.9 – 4.5	<0.001
Procedure Performed						0.01
	Neutering	0	1	0		
	Dental	2	5	0.6	0.1 – 3.8	0.44
	Diagnostics	14	22	1		
	Minor procedures	3	14	0.3	0.1 – 1.5	0.13
	Major procedures	63	57	1.7	0.8 – 3.7	0.15
	None	17	0			
Procedure Intended	Minor	26	44	1		
	Major	73	55	2.3	1.2 – 4.1	0.008
Procedure Difficulty						<0.001
	Simple	18	31	1		
	Moderate	37	43	1.5	0.7 – 3.1	0.29
	Difficult	20	20	1.7	0.7 – 4.1	0.21
	Very difficult	7	3	4.0	0.9– 18.6	0.05
	No procedure	17	0			
	Unknown	1	2			
Recumbency						0.33
	Lateral	16	15	1		
	Dorsal	62	55	1.1	0.5 – 2.3	0.89
	Sternal	7	5	1.3	0.3 – 5.1	0.70
	Multiple	14	24	0.6	0.2 – 1.5	0.22
Duration intended						0.95
	0-29 min	7	8	1		
	30-59 min	33	33	1.1	0.4 – 3.5	0.82
	60-89 min	30	25	1.4	0.4 – 4.4	0.59
	90 – max	29	32	1.0	0.3 – 3.2	0.95
	Unknown	0	1			
Induction Time						0.31
	8 am - 12 pm	45	52	1		
	12 pm - 5 pm	37	37	1.2	0.6 – 2.1	0.64
	5 pm – 8 am	17	10	2.0	0.8 – 4.8	0.13

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column.

+'Trend' represents the OR for a one-category increase in the variable.

Table 6.7.d The association of anaesthetics with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
General Anaesthesia or Sedation	General anaesthetic	94	92	1		
	Sedation	5	7	0.7	0.2 – 2.3	0.55
Premedication+						0.01
	None	37	19	1		
	Acepromazine	29	56	0.3	0.1 – 0.6	<0.001
	Medetomidine	3	2	0.8	0.1 – 5.1	0.79
	BZ / Opioids only	30	22	0.7	0.3 – 1.5	0.37
Induction agents						0.16
	Thiopentone	3	6	1		
	Propofol	81	83	12.0	0.5 – 8.1	0.35
	Medetomidine	2	4	1.0	0.1 – 9.7	1.00
	Mask induction	9	2	17.1	0.8 – 102.8	0.03
	Other	4	4	5.7	0.3 – 15.5	0.50
Inhalation Agent						0.03
	Isoflurane	70	86	1		
	Halothane	11	5	2.7	0.9 – 8.3	0.07
	Sevoflurane	5	1	6.1	0.7 – 55.5	0.07
	None	13	7	2.8	0.9 – 6.1	0.09
Induction and Maintenance Combinations						0.20
	Injectable/Isoflurane	63	80	1		
	Injectable/Halothane	11	5	2.8	0.9 – 8.6	0.06
	Injectable/Sevoflurane	2	1	2.5	0.2 – 29.0	0.44
	Injectable Only	13	7	2.4	0.9 – 6.3	0.08
	Inhalational Only	10	6	2.1	0.7 – 6.2	0.16
ET Intubation	No ET tube	8	7	1		
	ET tube	91	92	0.9	0.3 – 2.5	0.79
Oxygen	No Oxygen	4	5	1		
	Oxygen	95	94	1.3	0.3 – 4.9	0.73
Nitrous oxide	No nitrous oxide	88	77	1		
	Nitrous oxide	10	20	0.4	0.2 – 1.0	0.04
	Unknown	1	2			
Ventilation	Spontaneous	74	91	1		
	Controlled	25	8	3.8	1.6 – 9.3	0.01
Perioperative fluids						<0.001
	No fluids	12	17	1		
	Intravenous Catheter	1	15	0.1	0.0 – 1.0	0.01
	Fluids	86	67	1.8	0.8 – 4.1	0.14

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column. + Includes combinations of premedicant with other drugs (e.g. opioids).

Table 6.7.e The association of monitoring variables with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Monitoring person	Vet	30	21	1.6	0.8 – 3.1	0.15
	Nurse	69	78	1		
Other duties of monitor						0.64
	No other duties	81	77	1		
	Performing the op	3	5	0.6	0.1 – 2.5	0.45
	Assisting the op	14	17	0.8	0.4 – 1.7	0.55
	Unknown	1	0			
Record	No record	49	46	1		
	Record	45	53	0.8	0.5 – 1.4	0.43
	Unknown	5	0			
Pulse monitored	No pulse	24	23	1		
	pulse monitored	75	76	1.0	0.5 – 1.8	0.87
Respiratory rate monitored	No respiratory rate	13	7	1		
	Respiratory rate	86	92	0.5	0.2 – 1.3	0.16
Pulse oximeter used	No Pulse oximeter	39	35	1		
	Pulse oximeter	60	64	0.8	0.5 – 1.5	0.86
Capnography used	No Capnograph	80	87	1		
	Capnograph	19	12	1.7	0.8 – 3.8	0.17
Arterial Blood Pressure						0.75
	None	86	89	1		
	Direct	3	3	1.0	0.2 – 5.3	0.97
	Indirect	10	7	1.5	0.5 – 4.1	0.45
ECG	None	80	84	1		
	ECG	19	15	1.3	0.6– 2.8	0.45

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column.

Table 6.7.f The association of recovery and personnel factors with anaesthetic-related death in Sick Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Recovery Quality						<0.001
	Good	13	75	1		
	Moderate	11	16	4.0	1.5– 10.9	0.004
	Poor	6	2	17.3	2.6– 114.2	<0.001
	Unknown	2	6			
	No full recovery	67	0			
Recovery observed						0.92
	Continuously	21	47	1		
	Every 5 minutes	10	26	0.9	0.4 – 2.1	0.74
	10 minutes +	10	21	1.1	0.6 – 2.7	0.99
	Unknown	2	5			
	No recovery	56	0			
Rectal Temperature Taken (postoperative deaths only)	No	32	68	1		
	Yes	13	31	0.9	0.4– 1.9	0.77
	Unknown	1	0			
Veterinary Surgeon familiarity with Anaesthetic	Very familiar	80	83	1		
	Familiar or	13	14	1.0	0.4 – 2.2	0.93
	Unfamiliar	6	2			
	Unknown					
Veterinarian type						0.22
	Senior	46	37	1		
	Veterinarian	48	60	0.6	0.4– 1.2	0.13
	Junior	4	2	1.6	0.3– 9.4	0.59
	Veterinarian Locum	1	0			
	Unknown					
Veterinarian Postgraduate qualifications						0.74
	None	62	65	1		
	Anaesthesia	4	6	0.7	0.2– 2.6	0.59
	General	31	28	1.2	0.6– 2.2	0.64
	Unknown	2	0			
Anaesthetist Familiarity with Anaesthetic	Very familiar	84	74	1		
	Familiar or					
	Unfamiliar	13	16	0.7	0.3 – 1.6	0.41
	Unknown	2	9			
Anaesthetist type						0.29
	Vet	29	20	1		
	Nurse	54	58	0.6	0.3 – 1.3	0.20
	Unqualified person	16	21	0.5	0.2 – 1.3	0.15

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of the 'P Value' column.

6.3.2.2 Multivariable Model

Health status and procedure urgency remained important variables on which to build the model (Table 6.8). Patient weight, inhalation agent, ventilation type and preoperative blood tests were included in the model based on their low likelihood ratio p values. A significant interaction between ASA grade and preoperative blood tests was detected and was retained in the model. Clustering by clinic identity was not significant and was not retained in the model (p=1.0).

Table 6.8 Final logistic regression model of the risk of anaesthetic-related death in Sick Dogs

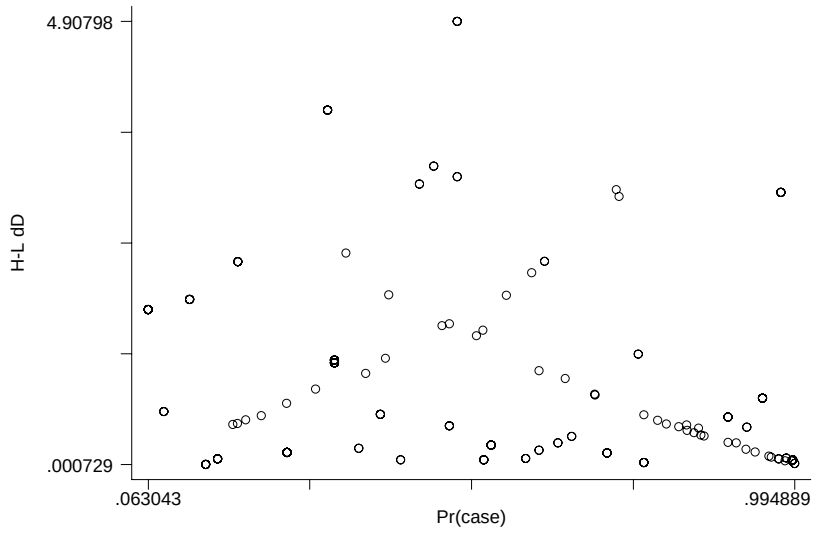
Variable	**Categories**	**β**	**s.e. β**	**OR***	**95% CI***	**P value**
ASA grade	ASA 3					
	ASA 4 – 5	3.61	1.14	37.2	4.0 – 346.2	<0.001
Preoperative bloods	No bloods			1		
	bloods	-0.33	0.49	0.7	0.3 – 1.9	0.02
ASA grade X Preoperative bloods		- 2.35	1.31	0.09	0.01 – 1.0	0.02
Urgency	Scheduled					
	Urgent					
	Emergency					
	Trend+	0.73	0.35	2.1	1.1 – 4.1	0.007
Categorical Weight	0-5 kg	1.95	0.64	7.1	2.0 – 24.7	
	5-15 kg			1		
	15- max	0.93	0.39	2.5	1.17 – 5.49	0.002
Inhalation Agent	Isoflurane			1		
	Halothane	1.58	0.54	4.9	1.7 – 14.0	
	Sevoflurane	0.34	0.85	1.4	0.3 – 7.4	
	None	0.40	0.51	1.5	0.6 – 4.0	0.08
Ventilation	Spontaneous			1		
	Controlled	1.21	0.56	3.4	1.1 – 10.0	0.02
Intercept		-3.10	0.85			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with corresponding Likelihood Ratio Test (LRT) P values. Number of observations 197 out of 198. +'Trend' represents the odds ratio for a one-category increase in the variable.

The model goodness of fit as assessed by the Hosmer – Lemeshow statistic was adequate (P value = 0.38) (Hosmer and Lemeshow 2000). Additional assessment of

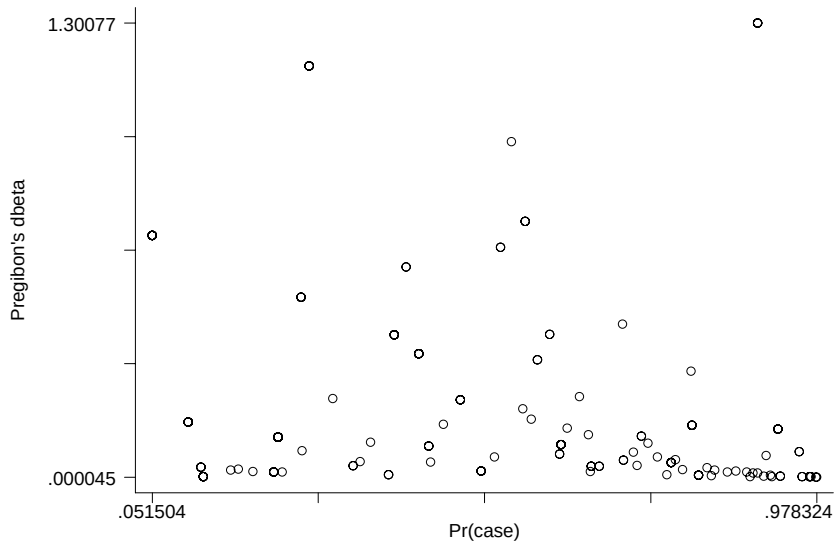
model with the regression diagnostic delta deviance, also suggested good model fit, with only 3 covariate patterns having delta deviances greater than 4 (Figure 6.3). Evaluation of the delta beta diagnostic statistic identified 9 covariate patterns with a delta beta greater than 1.0 (Figure 6.4). These observations were checked for errors and none found. When the model was rerun without these nine covariate patterns, health status and its interaction with preoperative blood tests were affected due to the subsequent presence of zero cells in the contingency table. Other parameter estimates did change, though were generally of a similar order and direction. Further the covariate patterns remained biologically plausible and were retained in the model.

Figure 6.3 The Delta Deviance diagnostic statistic versus the estimated probability for the Sick Dog Model



*H-L dD, Hosmer-Lemeshow delta deviance diagnostic statistic. Pr(case), probability of being a case. J=78 covariate patterns.

Figure 6.4 The Delta Beta diagnostic statistic versus the estimated probability for the Sick Dog Model



*Dbeta, Delta Beta diagnostic statistic. Pr(case), probability of being a case. J=78 covariate patterns.

Hence after adjusting for other variables increasing ASA grade, low patient weight, increasing procedure urgency, maintenance of anaesthesia other than with isoflurane and controlled ventilation were associated with increased odds of anaesthetic-related death. Preoperative blood tests were associated with reduced odds (Table 6.8).

6.4 Discussion

This chapter has identified a number of potential contributors to anaesthetic-related death in Dogs. Patient health status and weight, and procedural urgency were useful factors for aiding patient assessment in both Dogs and Sick Dogs. The choice of inhalation agent used was a modifiable factor retained in both models and may allow reduction in risk. In the overall Dog Study procedure complexity and duration, and patient age were further factors potentially useful to aid patient assessment, whilst in Sick Dogs, the method of ventilation and the use of preoperative blood tests may contribute to reduced risk.

6.4.1 Methodological Considerations

In assessing the validity of the reported models and the conclusions drawn, it is necessary to evaluate the limitations of the methodology and given these limitations, assess how well the model explains the data.

6.4.1.1 Study Design and Conduct

Case definition and selection were important considerations in evaluating the limitations of this Study (Hennekens and Buring 1987). The definition of anaesthetic-related death was potentially open to variable interpretation and inconsistent categorisation by participating centres. Due to this concern, centres were required to return a case-control questionnaire for all perioperative deaths within 48 hours of anaesthesia unless there was clear evidence of no role of anaesthesia. Additionally the primary investigator cross-checked all case-control questionnaires against the cohort diary (Chapter 2) to ensure all perioperative deaths had case-control questionnaires submitted or if no form was returned that there was sufficient information to exclude them from being considered cases. For those deaths where no case-control questionnaire was returned, the primary investigator contacted the centre to confirm anaesthesia did not contribute and requested a form if there was any doubt. This allowed a spectrum of deaths to be considered by the independent review panel (see Chapter 2), without the loss of potential cases. The independent review panel classified all cases against a strict list of criteria (Appendix 2.4) in order to increase consistency of classification. Issues of bias in selecting cases were minimised by using a population-based design and attempting to include all cases in the population (Hennekens and Buring 1987).

The controls should represent the population of individuals that would have been identified and classified as cases had they developed the outcome (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Given the population from which the cases were derived was known (i.e. the cohort); randomisation of the controls across the cohort should have provided representative controls. In the Sick Dog study, the specific cohort of sick dogs was not known, as health status was not recorded in the cohort diary. Hence it was assumed that the population of sick dogs would follow a similar distribution, across clinics and clinic workload, to the overall cohort and the sick dogs were randomised as for the overall controls. The exact distribution of sick dogs may

have varied, with some centres (e.g. referral institutions) anaesthetising more sick dogs than others. However the majority of centres were primarily first opinion (95%), and as such were more likely to see a similar distribution of sick dogs.

Selection bias, with differential selection of controls on the basis of their exposure histories, was a potential concern (Hennekens and Buring 1987). Given the intended inclusion of all cases this was less of a concern in the cases. However it was a potential issue for the controls and in this study it was minimised by randomising the controls across the cohort of patients anaesthetised and sedated (see Chapter 2) (Breslow and Day 1980; Dohoo, Martin et al. 2003). Differential patient management due to the process of being studied, the Hawthorne effect (Mangione-Smith, Elliott et al. 2002; Dohoo, Martin et al. 2003), was also a potential source of bias, and was minimised by prospectively requesting the controls, soon after each anaesthetic had been undertaken.

The issue of non-response was a consideration. The response rate for the cases was good: of 287 deaths recorded in the cohort study, only for 15 deaths (5%) was there insufficient information to exclude them from being cases. The low non-response rate in the cases should have limited its' potential bias on the results (Dohoo, Martin et al. 2003). The response rate for the controls of 82% for the Dog Study was considered good based on a suggested aim of a non-response rate of less than 20 to 30% (Dohoo, Martin et al. 2003). Nonetheless, the 18% of non-returned controls could have biased the results if the non-returned controls' exposure histories differed markedly from the recorded control population (Dohoo, Martin et al. 2003). A random sample of 20% of these non-responders generally indicated similar exposure histories for major risk factors compared to the returned controls. However there was a significant tendency for non-returned controls to be more likely to be emergency or urgent (versus scheduled) and to be sedation versus general anaesthesia compared to returned controls. That non-responding controls were more likely to be emergency or urgent, would suggest the odds of being an urgent or emergency procedure in the controls was underestimated and hence the reported increasing odds of death with increasing urgency may have been over-estimated. Similarly the tendency to reduced odds with sedation versus general anaesthesia would have been underestimated if more sedations were non-responding controls than anaesthetics. The latter effect may have contributed to the non-significance of this finding. However this was a sample of 20% of non-responders

and though a random sample, by chance it may not have been representative of all non-responders. The tendencies discussed above were not found in the Cat study (Chapter 7) and hence over-interpreting this potential bias should be cautioned. The lower response rate of 51% in Sick Dog studies was of greater concern however and these results must be interpreted more cautiously. Substantial non-response bias could have occurred. Some of these non-responders resulted from the practice not having an appropriate patient within the previous 2 to 3 weeks, however, a number would have been patients for which a questionnaire was not returned. Assessing the direction of bias was more difficult in this group because individual sick patients could not be directly identified from the cohort data as health status was not recorded in the cohort. Hence the risk factors identified in this population must be treated as preliminary findings.

Information or observation bias, particularly errors of misclassification, was a further potential concern (Breslow and Day 1980; Dohoo, Martin et al. 2003). Misclassification of exposure histories by the participating centres, was minimised by checking the case-control questionnaires against anaesthetic record forms when available, and by assessing the plausibility of the data. Data entry errors were minimised by checking the data twice and randomly checking 20% of the entered data again. In these random checks less than 5% of the cases and controls had an error. Misclassification of outcome was reduced by appointing an independent review panel to assess the potential cases, against a specific criteria list (Chapter 2). Recall bias was minimised by requesting the controls soon after the anaesthetic was undertaken, such that both case and control questionnaires would have been completed in the immediate days after the event whilst still fresh in the minds of those completing the questionnaires (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Further, the majority of the important information required for the forms would have been recorded in the practices' patient records. Hence efforts to minimize misclassification were made, and if they occurred the likelihood was that they were primarily non-differential in nature and at worst biased the measured odds towards unity (i.e. underestimated associations) (Dohoo, Martin et al. 2003).

6.4.1.2 Analysis

In the model building process, the likelihood ratio test statistic (LRT statistic) was preferred to the Wald test statistic when interpreting the significance of independent variables. The Wald test has been reported to be less reliable and consistent

compared to the LRT statistic, particularly for small sample sizes, and hence the latter approach was used (Hauck and Donner 1977; Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003).

The issue of missing case-control data would primarily be a concern if omissions were non-random and biased the results (Breslow and Day 1980; Katz 1999). Efforts were made at the Study conduct stage to minimised missing data, but some data remained unknown. At the univariable level, separate categories for unknown values were created for categorical variables, allowing inclusion of this data and assessment of potential associations of the unknown categories with outcome. Variables with large numbers of missing values were not included in the multivariable analysis. For example postoperative temperature was incompletely answered and was omitted from the multivariable analysis. Other variables with fewer missing values were considered in the multivariable analysis but where there was a choice of variables with similar LRT P values, the more complete variable was selected. If variables are retained in the final model with missing values, some authors suggest reporting the univariable analysis with the reduced data set (Katz 1999). The alternative of reporting the number of missing values in the final multivariable model and retaining them in the univariable analysis was preferred, as the missing values tended to occur in a few variables only (e.g. age) (Breslow and Day 1980; Schlesselman 1982; Katz 1999).

Specific numerical problems have been reported during logistic regression analysis, and of particular concern are zero cells in the contingency tables, covariates that complexly separate the outcome groups, and collinearity of the data (Hosmer and Lemeshow 2000). The problem of zero cells in the contingency cells was dealt with by collapsing categories with zero cells and sparse data (Hosmer and Lemeshow 2000). This was done at the univariable and multivariable stages for a number of variables. For example ASA grade 5 was only reported in the cases, not the controls (as expected) hence this category was combined with ASA 4 at the univariable stage. Similarly for a number of categorical variables with sparse data in specific categories, some categories were combined in anticipation of zero cells at the multivariable stage. Collinearity was observed between some variables and where possible the variables were combined, or only the biologically more valuable variable was retained (Katz 1999; Hosmer and Lemeshow 2000). The conceptual framework developed *a priori* (Chapter 2) also

informed on the likelihood of correlation between variables and helped identify overlap between variables. This aided the decision making on which variables were retained in the model building process. For example procedure difficulty was recorded as well as procedure type. These were considered likely to be not independent, and as such procedure type (intended procedure) was retained in the model and procedure difficulty excluded.

Concerns of confounding were addressed by measuring and adjusting for the anticipated variables in the multivariable analysis (Breslow and Day 1980; Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Previous work in small animals (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Brodbelt, Hammond et al. 2005), and the Pilot Study of the present study (see Chapter 2), identified health status as a major source of confounding and this was the key variable to adjust other factors by. The issue of residual confounding remained for certain variables where incomplete adjustment for the confounder could be made. Residual confounding will be discussed within the risk factor discussion. The potential for interactions was also addressed during the model building process and potential interactions were identified at the univariable stage by stratifying the results by major variables. In the final model two way interactions between independent variables were also assessed. In the main dog model no major interactions were identified whilst in the Sick dog the reported interactions were documented.

Methods of assessing model fit are important when evaluating the analysis performed. Model fit as assessed by the Hosmer Lemeshow goodness-of-fit test statistic (Hosmer and Lemeshow 2000) was good in both models. Visual evaluation of the respective tables of expected and observed deciles, supported reasonably good fit of both models (Dohoo, Martin et al. 2003). Further evaluation of the model with assessment of diagnostic statistics was also good. Regression diagnostics used to evaluate the influence of covariate patterns on the model and overall model fit, include delta deviance (Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003). Delta deviances greater than 4 or 5 are generally considered poorly fitting covariate patterns (Hosmer and Lemeshow 2000), and in both studies there were few large delta deviances. The delta beta diagnostic test statistic is a regression diagnostic that provides a summary measure of the influence of individual covariate patterns on the estimated

parameters (Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003). Covariate patterns with delta betas greater than 1.0 are said to be influential and should be investigated (Hosmer and Lemeshow 2000). The Dog study had no large delta betas and the Sick Dog study had only a few moderately influential covariate patterns. These patterns were considered biologically plausible and retained. Performing the analysis without the few moderately influential covariate patterns did not substantially affect the model coefficients, and it was concluded the models explained the data well (Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003).

Validation of the model, additional to assessing model fit, could have been undertaken by collecting new data or dividing the existing data set (Katz 1999; Hosmer and Lemeshow 2000). Collecting further data is preferred but as in the present study this was not feasible. Alternatives to this include split-group, jackknife and bootstrap methods, all variations of subdividing the dataset and re-evaluating the model with the smaller subgroups. These methods of model validation are particularly important to models predicting prognosis or diagnosis of disease but are rarely undertaken for studies identifying factors associated with an outcome whilst adjusting for confounders, as was the current work (Katz 1999; Dohoo, Martin et al. 2003).

6.4.2 Descriptive Data

The descriptive details from the Controls provided further information on trends in anaesthesia to complement and support the clinic level data reported in Chapter 3. The common use of acepromazine was consistent with clinic level data (Chapter 3), and previous reports (Clarke and Hall 1990; Dyson and Pettifer 1997; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001). The predominance of propofol use for induction in anaesthesia was also consistent with the clinic level data (Chapter 3) and more recent work in the USA (Wagner and Hellyer 2000), but contrasts with earlier work in the UK and elsewhere (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000; Nicholson and Watson 2001). Maintenance of anaesthesia was primarily with isoflurane, indicating similar trends in anaesthetic use in Dogs in practice in the USA and UK (Wagner and Hellyer 2000). Patient monitoring, as highlighted in the Chapter 3, was limited, with observation of pulse and respiratory rates being the principle methods used. Encouragingly, separate personnel generally monitored the patient and pulse oximetry was used in just over half of controls.

Other methods were used in only 10% of the controls. This was comparable to other recent veterinary practice-based work (Dyson and Pettifer 1997; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001), though contrasts with the more elaborate medical requirements of the minimum monitoring standards published by Eichhorn and colleagues and recommended by the American Society of Anesthesiologists (1986).

6.4.3 Risk Factors in the Dog Study

Patient health status, as described by the ASA Grade (Anon 1963), was an important factor associated with anaesthetic-related death, with a 6-fold increase in odds seen with an increase of one increment in patient status. The observation of increased risk with poorer health status was valuable in quantifying the risks and for identifying patients that need particularly careful perioperative management and provided further evidence of its relevance to veterinary species. Further, within the model, health status was a major confounder to adjust for. The association with health status has been consistently reported in other species within this study (Chapters 5 and 7), in other small animal studies (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Brodbelt, Hammond et al. 2005), in horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati, Ruzzi et al. 2004). Anaesthetic agents cause cardiopulmonary depression and the presence of pre-existing pathology is likely to predispose to greater anaesthetic-induced physiological disturbance (Hall, Clarke et al. 2001).

Procedural urgency was also an important factor to adjust other variables by, and potentially is an important predictive factor. Increasing urgency by one increment (scheduled to urgent to emergency) was associated with a 2.5 fold increase in odds. Though a component of the effect of urgency could reflect residual confounding by health status, given the small number of categories of ASA grade, the magnitude to

of effect suggests a genuine association. Increased risk has been associated with emergency procedures in the human and equine literature, though not in small animals (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Pedersen, Eliasen et al. 1990; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). Urgency could reflect the ability to thoroughly assess and stabilise the patient preoperatively, as well as personnel staffing levels (many emergency and urgent procedures would be done with less support staff) and personnel fatigue (emergency procedures were often performed in the night by staff having worked during the day).

The association of increasing odds of anaesthetic-related death with increasing age, with dogs 12 years or older being approximately 10 times more likely to die than young dogs, was an interesting finding suggesting age per se and not the tendency to poorer health status, to be a factor for anaesthetic-related death. Again residual confounding by health status could have contributed to the increased odds, but was unlikely to explain the majority of the ten–fold increase in odds for older dogs reported. There was a tendency to an interaction between health status and age such that the greatest increase in odds in old patients was in the healthy patients (ASA 1-2) though it was not retained in the model as it was not statistically significant. The latter observation was supported however by the lack of an association with age in the Sick dog model. Nonetheless the increasing odds with old age is supported by work in a referral population of dogs, that demonstrated old age being associated with perioperative death (Hosgood and Scholl 1998). Other small animal studies were unable to demonstrate this, though this may have been the result of their limited power more than a lack of an association (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Brodbelt, Hammond et al. 2005). Work in horses also supported this association (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004), and in human anaesthesia the risk associated with increasing age has been well documented (Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati,

Ruzzi et al. 2004). Biologically, the association is supported by the tendency for old patients to be more susceptible to the depressant effects of anaesthetics, to hypothermia via impaired thermoregulatory mechanisms and to prolonged recoveries due to tendencies to reduced metabolic function and hypothermia (Waterman 1981; Dhupa 1995; Meyer 1999; Hall, Clarke et al. 2001).

Patient weight was also associated with anaesthetic-related death, with patients under 5 kg being 7 times more likely to die. A component of this association could be residual confounding by age in particular as the younger patients would generally be the smallest though this is not established. In dogs, the association has not been reported previously, though small patients do tend to an increased risk of hypothermia (Waterman 1981; Dhupa 1995; Murison 2001). Smaller patients could also have been prone to drug overdose, as small errors in estimation of patient weight or drug dose calculation would have had greater effects than in larger patients. There was a tendency for breed being associated with outcome and in part this may relate to certain breeds being at increased odds due to their small size. However, breed was not entirely confounded by weight and was not included in the final model more due to insufficient study power to assess a large number of breeds. Non-significant tendencies to increased odds were seen with brachycephalic breeds (as represented by toy and utility breeds) and previous work has also suggested increased risk with brachycephalic breeds (Clarke and Hall 1990).

Intended procedure was retained in the final model with major procedure patients being 5.2 times more likely to die than minor procedure patients. A more specific categorisation was significant at the univariable level (Table 6.5c), but the large number of categories in this version was limited by model power and problems of zero cells in the contingency table (Hosmer and Lemeshow 2000). Intended procedure was preferred to actual procedure due to the problem of categorising those patients that died prior to a procedure (28 cases). Categorising these patients separately was difficult as it suggested an increase in odds if no procedure was performed, whilst excluding them would have excluded a significant stratum of patients. Intended procedure represented a predictive variable and could be valuable in aiding preoperative assessment of the odds of death based on the anticipated complexity of the procedure. Further, it approximated to actual procedure and could indicate the likely association with actual procedure an outcome. A component of this association could have reflected residual confounding by duration

of anaesthesia with intended major procedures reflecting increased odds due to the intended longer duration, but given both variables were retained in the model it was unlikely to explain the entire effect reported. The association of procedure complexity has been reported before in rabbits in this study (Chapter 5), in equine anaesthesia (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). A procedural association was likely to reflect the increasing stress more complex and invasive procedures imposed on patient physiology. More complex procedures may result in greater fluid and blood loss, exposure of body cavities and a tendency to greater hypothermia.

Increasing intended duration of anaesthesia was another important factor with odds increasing 1.06 times for each ten-minute increase in intended duration. The problem of intraoperative deaths made assessment of actual duration more difficult. Intraoperative deaths had shorter durations of anaesthesia than intended, consequently reducing the duration of anaesthesia in the cases and the association of increasing odds with increasing duration. To adjust for this, the intended duration was estimated for intraoperative deaths, based on the mean duration of controls in the same procedural category (Table 6.5c). Alternatively, only postoperative deaths could have been considered but this would have reduced the power of the study. Survival analysis could have been considered as seen in a study of long term outcome in man (Monk, Saini et al. 2005) and as was preliminarily undertaken in the CEPEF Study (Johnston, Taylor et al. 1996), however there was insufficient cohort data in the current study to undertake this. The intended variable thus was primarily a predictive variable such that intended duration predicted longer actual durations. Increasing odds with increasing intended duration would thus aid assessment of risk prior to anaesthesia and would also support a tendency to increased odds with increasing actual duration of death. The association of increasing intended duration and risk was seen in rabbits in the present study (Chapter 5) and increasing risk with increasing actual duration has been reported previously in horses (Trim, Adams et al. 1988; Young and Taylor 1990; Young and Taylor 1993; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and man (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Biboulet, Aubus et al. 2001; Newland, Ellis et al. 2002). Prolonged anaesthesia predisposes to hypothermia (Waterman

1981; Dhupa 1995) and longer periods of cardiopulmonary depression, were likely to have greater effects than short period, by increasing cellular metabolic derangement and damage (Hall, Clarke et al. 2001).

Maintenance and induction agent combinations were retained in the model with the major associations being approximately 6-fold increases in odds associated with halothane maintenance and total inhalational anaesthesia compared to injectable induction and isoflurane maintenance. The 71-fold increase in odds with injectable anaesthesia was likely to reflect those patients that died prior to maintenance with an inhalational agent. Of twelve cases that were anaesthetised with only injectable agents, 11 died before a procedure was performed and only 4 controls were maintained with injectable anaesthetics. Hence a true association with injectable anaesthesia was difficult to assess.

The increased odds with halothane contrasts with previous small animal work that suggested halothane was associated with reduced odds of complication (Dyson, Maxie et al. 1998), though is consistent with a randomised trial, in which isoflurane was associated with reduced odds in young horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004). The increased odds reported in the small animal study may have resulted from residual confounding by health status such that veterinary surgeons were less likely to choose halothane for sicker patients, and though the results were adjusted for ASA grade, only the binary variable was used (ASA 1-2 versus ASA 3-5). Though isoflurane induces greater respiratory depression and vasodilation than halothane, it causes less direct myocardial depression, and sensitises the heart less to catecholamine-induced arrhythmias and on balance would appear to cause less overall cardiovascular depression (Joas and Stevens 1971; Steffey, Gillespie et al. 1975; Steffey and Howland 1977; Hellebrekers 1986; Tranquilli, Thurmon et al. 1988; Grandy, Hodgson et al. 1989; Lemke, Tranquilli et al. 1993; Hikasa, Okabe et al. 1996; Hikasa, Ohe et al. 1997; Hodgson, Dunlop et al. 1998).

The increased odds with total inhalational anaesthesia is consistent with previous work in small animals and horses in which mask inductions have tended to increased risk of complications (Clarke and Hall 1990; Johnston, Taylor et al. 1995; Dyson, Maxie et al. 1998; Johnston, Eastment et al. 2002). Inhalational inductions potentially can be stressful, slower to reach tracheal intubation, and could induce greater

cardiopulmonary depression if excessive depth is reached prior to endotracheal intubation (Hall, Clarke et al. 2001). In a recent study mask inductions were associated with greater cardiopulmonary depression than injectable combinations in a population of high-risk patients (Mattson, Kerr et al. 2005).

It is interesting that the main intravenous induction agent appeared to affect outcome minimally. Though there is a perception in veterinary practice that propofol is a 'safe' drug (Wagner, Wright et al. 2003; Bilborough 2005), the cardiopulmonary profiles of propofol and thiopentone are similar (Glen 1980; Fahy, Mourik et al. 1985; Rolly and Versichelen 1985; Robinson, Sams et al. 1986; Sebel and Lowdon 1989; Turner and Ilkiw 1990; Branson and Gross 1994; Hall, Clarke et al. 2001). Dose effects were evaluated for the major drugs used, and there were consistent tendencies to reduced odds with increasing dose (Appendix 6.1). This was counter-intuitive given most of these agents exhibited dose-dependent cardiopulmonary depressant effects (Glen 1980; Fahy, Mourik et al. 1985; Robinson, Sams et al. 1986; Sebel and Lowdon 1989; Turner and Ilkiw 1990; Branson and Gross 1994; Hall, Clarke et al. 2001), and a major component of this observation was the result of confounding by health status, such that Sicker patients were generally administered smaller doses. However the associations observed were not completely confounded by health status, but they were not retained in the model due to limited Study power to evaluate these subpopulations and further work on dose effects is warranted.

Though there were tendencies to reduced odds with acepromazine and medetomidine (adjusted OR= 0.5, 95% CI 0.2 – 1.3 and OR=0.2, 95% CI 0.0 – 1.3 respectively), premedication did not improve the model (LRT p=0.3) and was not retained in the model. Acepromazine premedication has been associated with reduced risk in small animals and horses (Clarke and Hall 1990; Johnston, Taylor et al. 1995; Dyson, Maxie et al. 1998; Johnston, Eastment et al. 2002; Brodbelt, Hammond et al. 2005). The lack of a major association in the current model, may reflect in part limited power to detect significant associations for rare (and particularly common) exposures, as medetomidine was used for premedication in 5% of controls and acepromazine in 77% of controls. Case-control studies are more limited than cohort studies in their power to detect associations for rare exposures (Hennekens and Buring 1987). Further work is merited to evaluate the previous association of reduced odds with acepromazine.

Notwithstanding the above discussion, the tendency for reduced odds with the administration of medetomidine was an interesting observation, particularly as there was no evidence of increased risk. An older alpha$_2$ adrenoceptor agonist, Xylazine, was associated with increased risk in a number of small animals studies (Gillick 1981; Clarke and Hall 1990; Dyson, Maxie et al. 1998). The cardiopulmonary effects of the alpha$_2$ agonists include transient hypertension followed by hypotension, bradycardia, increased systemic vascular resistance, reduced cardiac output and minimal respiratory depression (Muir 1977; Greene and Tranquilli 1988; Savola 1989; Wagner, Muir et al. 1991; Cullen 1996; Ko, Bailey et al. 1996; Golden, Bright et al. 1998; Pyendop and Verstegen 1998; Pyendop and Verstegen 1999). Additionally, xylazine has been found to sensitise or not increase the threshold of the heart to catecholamine-induced arrhythmias under halothane anaesthesia (Muir, Werner et al. 1975; Tranquilli, Thurmon et al. 1986; Lemke, Tranquilli et al. 1993; Dyson and Pettifer 1997).

Though medetomidine's actions are similar to those of xylazine (Cullen 1996; Pyendop and Verstegen 1998; Pyendop and Verstegen 1999), medetomidine has not been found to sensitise the heart to catecholamine induced arrhythmias (Pettifer, Dyson et al. 1996). Combined with a greater awareness of the physiological effects of this group of drugs (in part due to the previous studies mentioned), and an improved understanding of how to use these drugs, it is plausible that medetomidine was associated with reduce odds. Clarke and Hall (1990) concluded that the majority of the complications with xylazine were associated with lack of familiarity with the agent, and their impact on subsequently administered induction agents. Hence, having assumed originally medetomidine would be associated with increased odds of anaesthetic-related death, this was not found in the current study. The odds tended to be reduced and were of a similar magnitude to that of acepromazine, another common premedicant. Medetomidine would appear a relatively safe premedicant, though given the relatively infrequent use of it as a premedicant in the current study, additional work would be merited to further quantify the potential for reduction in risk.

6.4.4 Risk Factors in the Sick Dog Study

Health status was consistently identified as a major risk factor in this project with poor health status patients being at particular risk of anaesthetic-related death. In light of the Pilot Study (see Chapter 2) and the small scale study undertaken in a referral

population (Brodbelt, Hammond et al. 2005), it was identified that the overall study population would generate insufficient poor health status controls to be able to evaluate associations in this important subpopulation carefully. Additionally it was thought the potential for improving patient outcome was particularly great in this group if important associations were identified. Hence this sub-study was undertaken.

Within the Sick Dog study, health status and procedure urgency were retained in the model, suggesting that in this more homogeneous population of high risk patients, increasingly poor health status and increasing urgency were still important determinants of outcome. The association with extremes of weight was also retained in the model, and biologically it would be expected that small high-risk patients would also be prone to increased odds of anaesthetic-related death due to greater risk of drug overdose and hypothermia (Waterman 1981; Dhupa 1995; Murison 2001). Further, overweight sick patients may also be less tolerant of anaesthesia, having poorer cardiopulmonary reserves (Hall, Clarke et al. 2001).

Premedication was not retained in the final model, though similar tendencies to reduced odds particularly with acepromazine, were seen at the univariable stage. That premedication was not included in the final model may also reflect limits of power. Inhalation agent was retained in this model, with isoflurane being associated with reduced odds, though after including the interaction between health status and preoperative bloods (see below) its LRT p value was just above 5%. On examining the residuals and model fit with and without this variable (see later), there were fewer large delta betas (delta betas >1.0: 9 covariate patterns versus 18) when inhalation agent was retained in the model, and combined with the near significance (p= 0.08), it was felt important to include this variable. Poorer health status patients would be expected to be particularly sensitive to the greater myocardial depression observed with halothane compared to isoflurane anaesthesia (Joas and Stevens 1971; Steffey, Gillespie et al. 1975; Steffey and Howland 1977; Hellebrekers 1986; Tranquilli, Thurmon et al. 1988; Grandy, Hodgson et al. 1989; Lemke, Tranquilli et al. 1993; Hikasa, Okabe et al. 1996; Hikasa, Ohe et al. 1997; Hodgson, Dunlop et al. 1998).

Mode of ventilation was a significant variable in this model. Confounding by procedure type, a variable not retained in the final model, could have contributed to this association with procedures performed under controlled ventilation being more

complicated and higher risk than those performed with spontaneous ventilation. However preliminary stratification and Mantel Haenzel adjustment of ventilation for major versus minor procedure yielded a similarly increased odds with controlled ventilation (Hosmer and Lemeshow 2000). Further, stratum specific odds for ventilation by procedure type indicated greater increased odds with controlled ventilation for minor compared to major procedures (minor procedures controlled ventilation OR= 7.4, 95% CI 1.5 – 37.6; Major procedures controlled ventilation OR=2.8, 95% CI 1.5 – 9.3). This would suggest an element of the increased odds with controlled ventilation in the major procedure group resulted from these being more complicated procedures, but in both strata the association remained. A direct effect on outcome however was also possible, controlled ventilation could induce greater cardiovascular depression than spontaneous ventilation, due to increased intra-thoracic pressure during inspiration decreasing venous return and filling of the heart, lower arterial carbon dioxide reducing sympatho-adrenal stimulation of the heart, and higher end-tidal inhalation agent inducing greater dose-dependent cardiovascular depression, due to more efficient delivery of the agent (Horwitz, Bishop et al. 1968; Cullen and Eger 1974; Steffey, Gillespie et al. 1974; Steffey, Gillespie et al. 1975; Thurmon, Tranquilli et al. 1996; Hall, Clarke et al. 2001).

Controlled ventilation without the use of muscle relaxants was commonly undertaken in these animals, as muscle relaxants are rarely used in veterinary anaesthesia and were used only in 2 cases and 5 controls in the Dog study and 2 cases and 2 controls in the Sick Dog study (approximately 1% of cases and controls). This contrasts with the use of muscle relaxants in human anaesthesia, where they are an integral part of balanced anesthesia and contribute to the provision of good surgical conditions whilst allowing a reduced level of inhalation agent (Minimum alveolar concentration or MAC sparring effect). The MAC sparring effects of muscle relaxants can reduce cardiovascular depression during anaesthesia (Hall, Clarke et al. 2001) and could be particularly relevant to reducing the impact of controlled ventilation on cardiovascular function in the poorer health status patients. The use of muscle relaxants could contribute to the observed differences in effect of method of ventilation observed in man and animals.

The association with preoperative blood testing, though not the basis of an *a priori* hypothesis, was interesting. There was significant heterogeneity within ASA grades for this association and the interaction was included in the model (Hosmer and

Lemeshow 2000; Dohoo, Martin et al. 2003). The association was not the result of confounding by procedure urgency as this was adjusted for in the model, and the percent of procedures that were urgent or emergency (92%) in the ASA 4-5 cases that did not have a blood test, was similar to that of the ASA 4-5 cases that did had a blood test (94%), suggesting the lack of a blood test was not the result of insufficient time to take one. Nor was there heterogeneity amongst the cases with respect to ASA grades 4 and 5, as in both ASA 4-5 cases that had and did not have a blood test, 39% were ASA 5 and 61% ASA 4. Further, the association did not result from more ASA 4-5 cases that did not have a blood test, occurring when there might have been reduced access to blood tests (i.e. weekend or the evening), as of 24 ASA 4-5 cases that did not receive blood tests, only 10 of them occurred overnight or on the weekend. Assuming the worst case scenario that all these cases would have had a blood test if they had had easy access to the tests, the revised crude odds of being a case in the ASA 4-5 stratum would still have been much lower to the odds in the ASA 3 stratum (ASA 4-5 OR=0.2, Exact 95% CI 0.0 – 1.1 versus ASA 3 OR 0.80, 95% CI 0.3 – 1.9). The biological significance of this observation could result from the particularly high-risk Sick patients (ASA 4-5), benefiting most from greater preoperative workup, preparation and stabilisation, than the less high-risk ASA 3 group. Interestingly, ASA 4-5 cases were over 3 times more likely to receive perioperative fluids if they had had a preoperative blood test.

Previous work is limited on the role of perioperative workup and risk, and the role of preoperative blood testing has proved contentious in veterinary anaesthesia (Hall, Clarke et al. 2001; Clutton 2005). The Association of Veterinary Anaesthetists, debated the merit of routine blood testing and concluded that routine blood tests were unlikely to improve patient outcome unless there was concurrent clinical evidence of pre-existing pathology (Hall, Clarke et al. 2001). A single centre study concluded routine blood testing was not warranted in terms of likely effect on patient management, (Alef, Von Praun et al. 2004). Hence though routine blood tests may not be justified, the results strongly suggest that preoperative blood tests in the higher-risk patients may be valuable and merit further investigation.

In summary, the associations identified in this poor health status subpopulation were similar to many of those reported in the overall Dog study. Patient health status and urgency remained important factors, as were patient weight and the inhalation agent

used. Additionally the model identified controlled ventilation and the presence of preoperative blood tests as associated with outcome and these factors warrant further evaluation. Issues of non-response in this sub-study however must caution the over-interpretation of these specific findings, and rather the results should form the basis of further work.

6.4.5 Causation and Association

The observed associations reported were unlikely to be explained by major bias or confounding. However the transition from association to causation remains difficult in observational studies (Schlesselman 1982). Hill (1965) described a number of criteria against which to assess the likely role of observed factors in the causation of an outcome. The strength of the association, consistency with other work, specificity of the association, temporality of the relationship, presence of a biological gradient, biological plausibility, coherence with the known biology of the disease or subject under study, presence of supporting experimental evidence, and presence of analogy to a similar condition are all criteria to base an assessment of the likely role of an association in causation (Hill 1965).

Based on these criteria patient health status, procedure urgency and complexity, patient age and the inhalation agent used, would appear to causally contribute to anaesthetic-related death. Patient health status has been consistently reported throughout this study in a number of species and in previously published work (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Clarke and Hall 1990; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Hosgood and Scholl 2002; Donati, Ruzzi et al. 2004; Johnston, Eastment et al. 2004; Brodbelt, Hammond et al. 2005). The association was found to be strong (OR=6.1), there was temporality of patient disease and subsequent outcome, there was a biological gradient (increasing odds with increasingly poor status), and the results were plausible and coherent with current knowledge. Its likely principal mode of influence, as suggested in the conceptual framework (Figure 2.1), involved

reduced tolerance of physiological disturbance induced by anaesthetic agents in the poorer health status patients, such that minor physiological depression could be converted to major depression and relative anaesthetic overdose.

Similarly, the association with urgency of the procedure has been reported across species in the current study and in previous work (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Pedersen, Eliasen et al. 1990; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). The magnitude of the association, though not as large as seen for health status was still biologically relevant (OR=2.5 for trend), and again there was a biological gradient for increased odds with increasing urgency, and there was appropriate temporality of urgency and outcome. Urgency was likely to reflect in part reduced ability to stabilise a patient and improve health status (see Figure 2.1, Chapter 2), but also it was likely to be related to personnel experience, given many emergency procedures occurred outside normal working hours. Hence the association was plausible and coherent with current understanding of anaesthesia and the risks associated with poor patient stabilisation prior to anaesthesia (Hall, Clarke et al. 2001).

The complexity of the procedure, represented by intended procedure, would appear also to contribute to anaesthetic-related death. This finding was demonstrated across species in the current study, and in previous work in equine anaesthesia (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). The association was strong (OR= 5.2), it was plausible, temporal and coherent with the current understanding of the physiological impact of surgery on anaesthesia (Clarke 1970; Hall, Young et al. 1978; Kehlet 1984). The relationship between intended and actual procedure was discussed in rabbits (Chapter 5), and intended procedure reflected both aspects relating to the impact of the procedure itself and the patient presenting for that procedure. Based on the conceptual framework (Chapter 2) the aspect pertaining to the patient presenting for that procedure, was likely to reflect in part the urgency of the procedure and patient health status, and as such there would be some overlap with these other factors. Nonetheless, an element of this association was

likely to reflect the impact of the procedure itself supporting its inclusion as a separate variable.

The association with age was consistent with work in a number of species (Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Johnston, Taylor et al. 1995; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Hosgood and Scholl 1998; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Donati, Ruzzi et al. 2004; Johnston, Eastment et al. 2004). There was a strong association, age exhibited a gradient of odds with increasing age, the association was plausible and it was consistent with the understanding of the physiological changes with age (Thurmon, Tranquilli et al. 1996). Hence, increasing age appears to causally contribute to the outcome.

The reduced odds ratio with isoflurane was a strong association and was consistently seen in both dog studies. Though it contrasted with a previous small animal study (Dyson, Maxie et al. 1998), it was consistent with results in young horses in a randomised controlled trial in horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and experimental studies of the two agents (Joas and Stevens 1971; Steffey, Gillespie et al. 1975; Steffey and Howland 1977; Hellebrekers 1986; Tranquilli, Thurmon et al. 1988; Grandy, Hodgson et al. 1989; Lemke, Tranquilli et al. 1993; Hikasa, Okabe et al. 1996; Hikasa, Ohe et al. 1997; Hodgson, Dunlop et al. 1998). Isoflurane induces less direct myocardial depression, and sensitises the heart less to catecholamine-induced arrhythmias and on balance would appear to cause less overall cardiovascular depression and reduce the risk of death.

Other factors observed in the Dog studies require further evaluation before concluding they causally contribute to anaesthetic-related death. These other associations were not based on *a priori* hypotheses and data-derived hypotheses should be interpreted cautiously (Hennekens and Buring 1987). The association with weight was reported in both the Dog and Sick Dog studies, and the magnitude of increased odds was large with low weight. Though the association has not been documented in small animals previously, small patients would be at a greater risk of hypothermia (Waterman

1981; Dhupa 1995; Meyer 1999; Hall, Clarke et al. 2001) and this could underlie the association. However, an element of the association could represent residual confounding by age, due to neonates being at increased risk due to their age whilst concurrently being smaller. Stratifying the odds for weight by age tended to increased odds in all categories of age, though the odds were greatest for the younger age categories, suggesting some residual confounding by age. Though plausible and based on a strong association the interdependence with age made a clear assessment of the role of weight difficult and further work is merited.

Increasing odds with increasing duration have been reported previously in horses (Trim, Adams et al. 1988; Young and Taylor 1990; Young and Taylor 1993; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004), in man (Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Biboulet, Aubus et al. 2001; Newland, Ellis et al. 2002) and also in rabbits in the current study. However the magnitude of this association was not great in the Dog Study and not retained in the final model in the Sick Dog Study. Though biologically plausible, based on the strength of association reported it would be premature to overstate the role of increasing duration on anaesthetic-related death. This association requires further work. The associations of preoperative blood testing and method of ventilation reported in Sick dogs, though biologically plausible and of a reasonable strength of association were not hypothesis-based and have not been reported in the small animal literature before. From the perspective of the conceptual framework (Chapter 2), preoperative blood testing was likely to reflect the urgency of procedure and the ability to stabilise the patient prior to anaesthesia, and as such some collinearity of these variables was likely in the Sick Dog study. Further, mode of ventilation could have impacted directly on outcome, but given procedure was not retained in the model, ventilation may well have reflected the impact of procedure more than the effect of controlled ventilation *per se*. Nonetheless, these are interesting observations but require further evaluation before concluding they causally contribute to anaesthetic-related death.

In summary, a number of factors were identified as potential contributors to the multi-factorial process of anaesthetic-related death in dogs. Severity of preoperative disease, procedural urgency and complexity, and age formed a useful core of variables to aid patient risk assessment preoperatively. Extremes of patient weight were associated

with increased odds and may assist patient assessment. Modifiable factors included inhalation agent and the use of isoflurane could reduce the risk of anaesthetic-related death compared to halothane. Preoperative blood testing may be valuable and the method of ventilation may affect outcome for higher risk patients, but these factors merit further investigation.

Chapter 7: Risk Factors for Anaesthetic-Related Death in Cats

7.1 Introduction

Factors associated with anaesthetic death in cats, like dogs, have been reported infrequently in the veterinary literature and not for nearly 20 years in the UK (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998) (see Chapter 1). The aims of this part of the study were to evaluate risk factors associated with anaesthetic-related death in cats and in a subpopulation of sick cats (ASA 3-5, see Chapter 2).

7.2 Materials and Methods

A case-control study was undertaken, nested within the cohort of cats anaesthetised and sedated at participating practices during the study period (see Chapter 2). A case was defined as a perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death or euthanasia was due solely to inoperable surgical or pre-existing medical conditions. A death was considered a case if anaesthesia or sedation could not be reasonably excluded as a contributory factor. All deaths from the cohort potentially fitting the case definition were evaluated by the independent review panel and classified against a list of criteria as case or not. Controls were randomly and prospectively selected during the study period from the cohort of anaesthetised and sedated cats at the participating centres at a 1:4 Case: Control ratio for the overall cat study ('Cat Study').

A sub-population of poor health-status cats was also evaluated ('Sick Cat Study'). All cases that were classified as 'Sick' (ASA 3-5, see Appendix 2.1), were included as cases in this section of the study. Controls for this study (Sick controls), were randomly and prospectively selected from the cohort of anaesthetised and sedated sick cats at the participating centres during the study period at a 1:1 Case: Control ratio.

Univariable analysis of the data was undertaken to determine the association of each variable with the odds of anaesthetic-related death. For categorical data, odds ratios (OR) were calculated and the 95% confidence intervals (95% CI) were calculated for the risk factors using the standard errors obtained as the square root of the variance

of the score statistic (Stata 7.0, Statacorp)(Breslow and Day 1980; Schlesselman 1982; Hosmer and Lemeshow 2000). Chi-squared test or Fisher's Exact test were applied to test the statistical significance of the associations for categorical variables where appropriate (Kirkwood 1988). Additionally, for multiple category variables, the likelihood ratio test P value was calculated for the variable to give an overall p value, comparing a logistic regression model with the variable included to that without the variable (Hosmer and Lemeshow 2000). When appropriate for multiple category variables, the odds ratio for a one category increase in odds was calculated (a one degree of freedom test for trend, 'trend')(Hosmer and Lemeshow 2000). For continuous variables, the Student's t test or Mann-Whitney U test, were applied (Kirkwood 1988).

The assessment of duration of anaesthesia was complicated by the fact that deaths prior to the procedure being undertaken tended to increase the odds associated with shorter duration of anaesthesia. To overcome this problem, "intended" duration of anaesthesia was estimated for cases that died before the procedure was performed, by using the mean duration for controls for the same procedure category as described by procedure performed (Table 7.5c). Intended procedure type was recorded in addition to actual procedure to allow categorisation of those cases that died prior to performing the procedure.

Biologically significant factors and variables significant at the 20% level were retained for evaluation in a mixed effects logistic regression model. Stratification of independent variables by potential confounders (e.g. health status) was performed to explore and identify multivariable associations and effect modification prior to multivariable analysis (Breslow and Day 1980). Logistic regression was then used and the statistical significance of the explanatory variables to the model was assessed using the log likelihood function (Hosmer and Lemeshow 2000). Variables significant ($p<0.05$) based on the likelihood ratio test statistic were retained in the logistic regression model using a forward selection approach (Dohoo, Martin et al. 2003). Variables with a large number of missing values were excluded from this approach, except when considered biologically important and then a separate category for missing or unknown values was created (Katz 1999). Biologically plausible first order interactions were assessed in the final multivariable model (Hosmer and Lemeshow 2000). Clustering at the clinic level was adjusted for, by using clinic identity as a random effect (Dohoo, Martin et al.

2003). The fit of the final models was assessed with the Hosmer Lemeshow goodness-of-fit statistic and by evaluating the models' residuals with the delta deviance and delta beta influence diagnostic statistics based on the observed covariate patterns (Hosmer and Lemeshow 2000).

7.3 Results

One hundred and seventy five deaths within 48 hours of anaesthesia or sedation were classified as cases in cats. Eighty-one cases (46%) were graded healthy (ASA 1-2) and 94 as sick (54%, ASA 3-5). During the study period 693 controls were requested in the Cat study, 557 were returned (80% response rate) and two were excluded (duplicates of other controls). This resulted in 555 controls being included in the analysis of the Cat Study (Case: Control ratio 1:3.2). Of the 555 controls, 47 were classified as Sick / ASA 3-5 (8.5% of Controls) and were included as Controls in the Sick Cat Study. An additional 127 Sick Controls were requested over the study period, 75 were returned (59% response rate) and 9 were excluded (1 was euthanased within 48 hours, 8 were ASA grade 2), resulting in 66 further Sick Controls. A total of 113 controls were compared to 94 cases for the Sick Cat Study (Case: Control ratio 1:1.2).

The cohort of cats anaesthetised and sedated (and not dying or being euthanased within 48 hours) during the study consisted of 9,625 sedations (12%) and 67,999 general anaesthetics (88%), in comparison in the case-control study 55 of 555 controls were sedations (10%), these proportions were not significantly different (P=0.06). Further, the Hauck-Anderson corrected 95% confidence intervals for the difference in proportions of sedated cats, between the case-control and cohort studies, were -5.1 to -0.0%, which would suggest reasonable equivalence (Tu 1997; Christley and Reid 2003). When comparing the cat controls to the non-returned controls (Table 7.1), health status, procedure urgency, sedation versus anaesthesia, age and major versus minor procedures were not significantly different and the 95% confidence intervals for the difference in proportions suggested reasonable equivalence between returned and non-returned controls (Christley and Reid 2003) and minimal non-response bias.

Table 7.1 Comparison of controls and non-returned controls in Cats.

Risk Factor	Proportion of controls	Proportion of non-returned controls	P value	95% CI* for the difference in proportions
Sedation	55/555 (9.9%)	2/23 (8.7%)	0.84	-15.5 to 13.1%
ASA 3-5	47/555 (8.5%)	3/23 (13.0%)	0.44	-12.0 to 21.1%
Urgent or Emergency	97/555 (17.5%)	2/23 (8.7%)	0.27	-23.2 to 5.7%
Major Procedure	35/555 (6.3%)	3/23 (13.0%)	0.20	-9.8 to 23.2%
Age**	5.3 +/- 5.1 years	4.1 +/- 4.1 years	0.27	-1.0 to 3.6 years

* 95% Confidence interval (CI) for the difference in proportion between the Controls and non-returned Controls. ** Mean and standard deviation are reported and the 95% CI for the difference between controls and non-returned controls.

7.3.1 Cat Study

The control population of cats had a mean age of 5.3 years (5.1 sd) with 48% male and 52% female. Domestic shorthairs (DSH) were commonly presented (82%), followed by Domestic longhairs (DLH) (8%), Persians (3%) and other Pure-breeds (6%). Neutering was the most common procedure performed (41%), followed by diagnostic procedures (20%), minor soft tissue procedures (21%) and dental surgery (11%, Table 7.5c).

Most control cats (71% of controls) were premedicated prior to anaesthesia (Table 7.2). Acepromazine combinations were most commonly used (63% of controls), 4% had medetomidine combinations prior to anaesthesia, 4% had benzodiazepine and opioid combinations and 29% had no premedication. Anaesthesia was induced primarily with propofol (51% of controls), followed by medetomidine and ketamine or medetomidine and opioid combinations (23%), thiopentone (11%), and Saffan (9%, alphadolone / alphaxalone) (Table 7.3). Medetomidine combinations were also commonly used for sedation (80% of sedations). Anaesthesia was generally maintained with isoflurane (59% of controls, Table 7.4). Thirty-four percent of patients were maintained with injectable agents only.

Table 7.2 Premedication given to Cats

Premedication	Cases*	Controls*
No Premedication	54 (31%)	159 (29%)
Acepromazine Combinations	90 (51%)	351 (63%)
Medetomidine Combinations	10 (6%)	22 (4%)
Benzodiazepine / Opioid Combinations	21 (12%)	23 (4%)
Total	175 (100%)	555 (100%)

* Number and percent of total (%).

Table 7.3 Induction agents used in Cats

Induction agent	Cases*	Controls*
Thiopentone	18 (11%)	63 (11%)
Propofol	114 (65%)	282 (51%)
Saffan	9 (5%)	52 (9%)
Medetomidine Combinations	18 (10%)	129 (23%)
Benzodiazepine / Ketamine Combinations	5 (3%)	13 (2%)
Mask Induction	7 (4%)	13 (2%)
Other Methods of Induction	4 (2%)	3 (1%)
Total	175 (100%)	555 (100%)

* Number and percent of total (%).

Table 7.4 Maintenance agents used in Cats

Maintenance Agent	Cases*	Controls*
Isoflurane	131 (75%)	327 (59%)
Halothane	5 (3%)	29 (5%)
Sevoflurane	3 (2%)	8 (1%)
Injectable Agents only	36 (21%)	191 (34%)
Total	175 (100%)	555 (100%)

* Number and percent of total (%).

Approximately 20% of control cats had intravenous catheters placed perioperatively and 15% received perioperative intravenous fluids. Intraoperative monitoring was undertaken primarily by a qualified veterinary nurse (56%). Thirty one percent had an unqualified nurse, 4% a separate veterinary surgeon and 9% having no separate person monitoring the patient. Thirty percent had a written record of the anaesthetic. Monitoring was primarily undertaken by monitoring patient pulse and respiratory rates (66% and 92% respectively), though the use of a stethoscope and pulse oximetry were also common (45% and 42% of controls respectively). Additional monitors were infrequently used, with only 4% of controls being monitored with capnography, arterial blood pressure monitoring and electrocardiography. Postoperatively, patients were generally observed by a nurse, though most were only checked every five minutes or more (33% continuously, 62% checked every five or more minutes). Postoperative temperature was only taken in 11% of controls.

The procedures were most often undertaken by a junior veterinary surgeon (63% of controls), whilst a senior veterinary surgeon undertook 31% of procedures and locum veterinary surgeons 6%. Eighteen percent (101 controls) of the procedures were undertaken by a veterinary surgeon with a non-anaesthesia postgraduate qualification, and 6% (34 controls) with a veterinary anaesthesia qualification (RCVS Certificate or Diploma, European Diploma, PhD). Of the 58 cat controls monitored by a veterinary surgeon, 57% (33 controls) were monitored by a veterinary surgeon with a postgraduate qualification in veterinary anaesthesia, and 2% (1 control) with a non-anaesthesia postgraduate qualification.

7.3.1.1 Univariable Associations

There was an increase in the odds of anaesthetic-related death with increasing, age (12 years and older, OR = 3.5, Table 7.5a). Both low and high patient weight were associated with increased odds compared to those weighing 2-6 kg (OR = 6.5 and 4.0 respectively). There were no breed associations. Patients having undergone previous anaesthetics or sedations in the last month also showed a tendency to increased odds (OR = 1.6). Preoperative disease was markedly associated with increased odds of anaesthetic-related death (Table 7.5b). A one category increase in poor patient health status (ASA grade 1-2, 3, 4-5)(Anon 1963) was associated with a 6.5-fold increase in odds. Performing preoperative blood and other tests prior to anaesthesia were

associated with increased odds (OR = 2.3 and 3.6 respectively), whilst withholding of food and water were associated with reduced odds (OR = 0.4 and 0.6 respectively).

Increasing procedure urgency was significantly associated with outcome (one category increase in urgency OR = 4.2, Table 7.5c) and more complex procedures and increasing procedure difficulty (assessed by the operating veterinary surgeon) were also associated with increased odds (Table 7.5c). Procedures undertaken in more than one position or not in lateral recumbency tended towards increased odds. Cases had significantly longer durations of anaesthesia than controls (cases 44.8 +/- 42.7 min, controls 34.1 +/- 29.8 min, $p<0.001$; mean and standard deviation (SD)) and increasing duration of anaesthesia was associated with an increased odds of death for procedures over 90 minutes (OR = 3.3). This association was more clearly seen with the intended duration (cases 50.3 +/- 40.7 min, controls 34.1 +/- 29.8 min, $p<0.001$, mean and SD). Late start times were associated with increased odds (procedures after 5 pm OR = 9.2).

Compared to not receiving premedication, having benzodiazepine or opioid premedication was associated with increased odds (OR = 2.7, Table 7.5d). Induction of anaesthesia with propofol, benzodiazepines and ketamine or by mask, tended to be associated with increased odds compared to thiopentone. Saffan and medetomidine/ketamine combinations tended towards being associated with reduced odds. Increasing doses of thiopentone and propofol were associated with reduced odds (Appendix 7.1). Injectable anaesthesia was associated with reduced odds compared to injectable induction followed by maintenance with isoflurane (OR = 0.5, Table 7.5d). Sedation compared to general anaesthesia tended to be associated with reduced odds (OR = 0.6). Endotracheal intubation (OR = 3.0), oxygen administration (OR = 3.0), receiving perioperative fluids (OR = 8.5) and controlled ventilation (OR = 10.6) were associated with increased odds.

Monitoring patient pulse and the use of pulse oximetry were associated with reduced odds (OR = 0.5 and 0.6 respectively), whilst using a stethoscope or measuring arterial blood pressure were associated with increased odds (OR = 1.6 and OR = 2.1 respectively). Time to sternal recumbency was longer in the cases (cases 57.8 +/- 112.1 min (n=44), controls 17.7 +/- 16.0 (n=470), $p<0.001$), postoperative temperature was lower in the cases (cases 35.9 +/- 1.3 ^{0}C (n=18), controls 36.8 +/- 1.1 ^{0}C (n=51), $p=0.006$), whilst less frequent patient monitoring postoperatively was associated

with reduced odds (observed every 5 or more minutes OR = 0.5, 95% CI 0.3 – 0.8). Procedures undertaken by a veterinary surgeon with a non-anaesthesia postgraduate qualification tended to be associated with increased odds of anaesthetic-related death (OR = 1.7, Table 7.5f).

Table 7.5.a The association of patient variables with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Categorical Age						<0.001
	0- 0.5 years	6	24	1.3	0.5 – 3.4	0.55
	0.5 – 5 years	54	287	1		
	5 – 12 years	59	153	2.0	1.3 – 3.1	<0.001
	12 years – max	56	84	3.5	2.2 – 5.6	<0.001
	Unknown	0	2			
Sex	Male	92	268	1		
	Female	83	287	0.8	0.6 – 1.2	0.32
Neutered	Entire	38	261	1		
	Neutered	129	285	3.1	2.1 – 4.7	<0.001
	Unknown	8	9			
Categorical						<0.001
Weight	0-2 kg	9	5	6.5	2.1 – 19.9	<0.001
	2-6 kg	144	518	1		
	6 - max	19	17	4.0	2.0 – 8.0	<0.001
	Unknown	3	15	0.7	0.2 – 2.5	0.61
Overweight	Not overweight	145	492	1		
	Overweight	25	36	2.4	1.4 – 4.1	0.002
	Unknown	2	27			
Scales used	Scales	135	421	1		
	Estimate	37	123	0.9	0.6 – 1.4	0.76
	Unknown	3	10			
Breed						0.82
	DSH	140	455	1		
	DLH	12	43	0.9	0.5 – 1.8	0.77
	Persian	7	19	1.2	0.5 – 2.9	0.69
	Other Pure Breed	16	35	1.5	0.8 – 2.8	0.20
	Unknown	0	3			
Primary Case	Primary patient	164	533	1		
	Referral patient	11	21	1.7	0.8 – 3.6	0.16
	Unknown	0	1			
Previous Sedations or Anaesthetics within the month	None	144	474	1		
	One or more	23	47	1.6	0.9 – 2.7	0.07
	Unknown	8	34			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values presented for multiple category variables at the top of 'P Value' column.

Table 7.5.b The association of patient variables with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Preoperative disease						<0.001
	None	15	304	1		
	Cardiopulmonary	49	34	29.2	12.5 –68.3	<0.001
	Neurological	2	4	10.1	1.7 – 61.6	0.002
	Digestive	55	90	12.2	6.2 – 24.6	<0.001
	Urogenital	22	20	22.2	8.8 – 56.2	<0.001
	Other	32	103	6.3	3.3 – 12.5	<0.001
ASA grade (ASA3)						<0.001
	ASA 1-2	81	508	1		
	ASA 3	42	39	6.8	4.0 – 11.4	<0.001
	ASA 4-5	52	8	40.8	16.3-101.9	<0.001
	Trend+			6.5	4.7 – 9.1	<0.001
ASA grade (ASA2)	ASA 1-2	81	508	1		
	ASA 3-5	94	47	12.5	7.7 – 20.3	<0.001
Preoperative examination	No	10	47	1		
	Yes	165	506	1.5	0.8 – 3.1	0.23
	Unknown	0	2			
	Adjusted ASA2**			0.9	0.4 – 2.0	0.83
Preoperative bloods	No	96	408	1		
	Yes	78	145	2.3	1.6 – 3.3	<0.001
	Unknown	1	2			
	Adjusted ASA2**			1.4	0.9 – 2.1	0.09
Other tests	No	109	476	1		
	Yes	65	78	3.6	2.4 – 5.4	<0.001
	Unknown	1	1			
	Adjusted ASA2**			1.6	1.0 – 2.6	0.06
Starved Preoperatively	No	7	9	1		
	Yes	151	529	0.4	0.1 – 1.0	0.04
	Unknown	17	17			
	Adjust for ASA2**			0.9	0.3 – 3.0	0.89
Water withheld	No	82	213	1		
	Yes	71	320	0.6	0.4 – 0.8	0.003
	Unknown	22	21			
	Adjust for ASA2**			0.8	0.5 – 1.2	0.31

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are presented for multiple category variables at the top of 'P Value' column. **ORs adjusted for health status (ASA2) are reported when confounded by health status.

+'Trend' represents the OR for a one-category increase in the variable.

Table 7.5.c The association of procedural variables with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Urgency						<0.001
	Scheduled	83	458	1		
	Urgent	67	89	4.2	2.8 – 6.3	<0.001
	Emergency	25	8	17.2	7.1 – 42.0	<0.001
	Trend+			4.2	3.1 – 5.7	<0.001
Procedure Performed						<0.001
	Neutering	10	228	1		
	Dental	31	111	6.4	2.9 – 13.9	<0.001
	Diagnostics	16	61	5.9	2.5 – 14.3	<0.001
	Soft tissue minor	36	118	7.0	3.2 – 15.0	<0.001
	Soft tissue major	40	17	53.6	16.4 – 175.2	<0.001
	Orthopaedics/ Neurological	11	20	12.5	4.4 – 35.8	<0.001
	None	31	0			
Intended Procedure	Minor	115	520	1		
	Major	60	35	7.8	4.7 – 12.7	<0.001
Procedure Difficulty						<0.001
	Simple	63	403	1		
	Moderate	54	135	2.6	1.7 – 3.9	<0.001
	Difficult / V Diff	27	15	11.5	5.5 – 24.1	<0.001
	No procedure	31	0			<0.001
	Unknown	0	2			
Recumbency						<0.001
	Lateral	58	291	1		
	Dorsal	44	56	3.9	2.4 – 6.5	<0.001
	Sternal	14	29	2.4	1.2 – 4.9	0.01
	Multiple	56	178	1.6	1.0 – 2.4	0.03
	Unknown	3	0			
Duration						<0.001
	0-29 min	76	283	1		
	30-59 min	48	182	1.0	0.7 – 1.5	0.93
	60-89 min	23	57	1.5	0.9 – 2.6	0.14
	90 –max	25	28	3.3	1.8 – 6.1	<0.001
	unknown	3	5			
Duration intended						0.29
	0-29 min	57	283	1		
	30-59 min	58	182	1.6	1.5 – 3.4	0.03
	60-89 min	32	57	2.8	2.1 – 6.2	<0.001
	90 –max	25	28	4.4		<0.001
	unknown	3	5			
Induction Time						<0.001
	8 am - 12 pm	84	414	1		
	12 pm - 5 pm	76	123	3.0	2.1 – 4.5	<0.001
	5 pm – 8 am	13	7	9.2	3.4 – 24.3	<0.001
	unknown	2	11			
	Trend+			3.0	2.2 – 4.2	<0.001

*Odds ratios (OR) and 95% confidence intervals (CI). Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value'. +'Trend' represents a one-category increase.

Table 7.5.d The association of anaesthetic agent with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
General Anaesthesia (GA) or Sedation	GA	164	500	1		
	Sedation	11	55	0.6	0.3 – 1.2	0.14
Premedication+						0.001
	None	54	159	1		
	Acepromazine	90	351	0.8	0.5 – 1.1	0.15
	Medetomidine	10	22	1.3	0.6 – 3.0	0.48
	BZ / Opioids only	21	23	2.7	1.4 – 5.3	0.003
Induction agents						<0.001
	Thiopentone	18	63	1		
	Propofol	114	282	1.4	0.8 – 2.5	0.23
	Saffan	9	52	0.6	0.2 – 1.5	0.26
	Medetomidine combinations	18	129	0.5	0.2 –1.0	0.05
	Benzodiazepines / Ketamine	5	13	1.3	0.4 – 4.3	0.62
	Mask induction	7	13	1.9	0.6 – 5.5	0.24
	Other	4	3	4.7	0.9 – 23.9	0.04
Inhalation Agents						0.001
	Isoflurane	131	327	1		
	Halothane	5	29	0.4	0.2 – 1.1	0.08
	Sevoflurane	3	8	0.9	0.2 – 3.6	0.92
	None	36	191	0.5	0.3 – 0.7	<0.001
Induction and Maintenance Combinations						0.003
	Injectable/Isoflurane	122	309	1		
	Injectable/Halothane	5	28	0.5	0.2 – 1.2	0.10
	Injectable/Sevoflurane	2	5	1.0	0.2 – 5.3	0.99
	Injectable Only	36	191	0.5	0.3 – 0.7	<0.001
	Inhalational Only	10	22	1.2	0.5 – 2.5	0.72
Endotracheal (ET) Intubation	No ET tube	27	135	1		
	ET tube	148	419	3.0	1.9 – 4.7	<0.001
Oxygen	No Oxygen	17	135	1		
	Oxygen	158	419	3.0	1.7 – 5.2	<0.001
	Unknown	0	1			
Nitrous oxide	No nitrous oxide	160	505	1		
	Nitrous oxide	14	47	0.9	0.5 – 1.8	0.84
	Unknown	1	3			
Ventilation	Spontaneous	149	545	1		
	Controlled	26	9	10.6	4.7 – 23.7	<0.001
	Unknown	0	1			
	Adjust ASA2**			3.5	1.4 – 8.9	0.005

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column.
+ Includes combinations of premedicant with other drugs (e.g. opioids).
**ORs are adjusted for health status (ASA2) when confounded by health status.

Table 7.5.e The association of management and monitoring factors with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Perioperative fluids						<0.001
	No fluids	65	439	1		
	IV Catheter only	5	33	1.0	0.4 – 2.7	0.96
	Fluids given	105	83	8.5	5.5 – 13.2	<0.001
Monitoring person						0.44
	Vet	21	58	1.0		
	Nurse	152	495	0.8	0.5 – 1.4	0.14
	No one	2	2	2.8	0.4 – 21.4	0.31
Other Duties of Monitoring Person						0.18
	No other duties	131	402	1		
	Performing the op	8	48	0.5	0.2 – 1.1	0.08
	Assisting the op	34	100	1.0	0.7 – 1.6	0.85
	Unknown	2	5			
Record	No record	97	379	1		
	Record	69	161	1.7	1.2 – 2.4	0.005
	Unknown	9	15			
Respiratory rate monitored	No respiratory rate	25	45	1		
	Respiratory rate	154	510	0.7	0.4 – 1.1	0.11
Pulse and pulse oximeter used						0.04
	None	49	100	1.0		
	Pulse only	56	223	0.5	0.3 – 0.8	0.003
	Pulseox only	27	91	0.6	0.3 – 1.0	0.07
	Pulse and pulseox	43	141	0.6	0.4 – 1.0	0.05
Stethoscope used	No Stethoscope	76	303	1		
	Stethoscope	99	252	1.6	1.1 – 2.2	0.01
Capnography used	No Capnograph	167	524	1		
	Capnograph	8	31	0.8	0.4 – 1.8	0.60
Arterial Blood Pressure	None	161	533	1		
	Indirect	14	22	2.1	1.1 – 4.2	0.03
	Adjust ASA2			1.4	0.7 – 2.9	0.34
ECG	None	163	532	1		
	ECG	12	23	1.7	0.8 – 3.5	0.14
	Adjust ASA2**			0.8	0.3 – 2.0	0.58

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category at the top of 'P Value' column. **ORs are adjusted for health status (ASA2) when confounded by health status.

Table 7.5.f The association of recovery and personnel factors with anaesthetic-related death in Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Recovery Quality						<0.001
	Good	39	377	1		
	Moderate	25	152	1.6	1.8 – 6.6	0.08
	Poor	16	3	51.5	6.8 –108.2	<0.001
	Unknown	3	23			
	No full recovery	92	0			
Recovery Observed						0.007
	Continuously	49	185	1		
	5 minutes +	45	345	0.5	0.3 – 0.8	0.002
	Unknown	3	16	0.7	0.2 – 2.5	0.59
	No recovery	77	0			
Postoperative Temperature Taken	No	79	487	1		
	Yes	26	63	2.5	1.5 – 4.3	<0.001
	Unknown	1	4			
	Intraoperative death	69	0			
Veterinary surgeon familiarity with anaesthetic	Very Familiar	164	496	1		
	Familiar or Unfamiliar	8	39	0.6	0.3 – 1.4	0.22
	Unknown	3	18			
Veterinary surgeon type						0.29
	Senior Veterinarian	62	169	1.2	0.8 – 1.7	0.32
	Junior Veterinarian	107	350	1		
	Locum	5	32	0.5	0.2 – 1.3	0.16
	Other	1	2	1.6	0.1 – 18.3	0.69
Veterinary surgeon postgraduate qualifications						0.07
	None	127	438	1		
	Anaesthesia	10	34	1.0	0.5 – 2.1	0.97
	General	38	78	1.7	1.1 – 2.6	0.02
	Unknown	0	5			
Anaesthetist familiarity with anaesthetic	Very familiar	137	435	1		
	Familiar or Unfamiliar	20	77	0.8	0.5 – 1.4	0.451
	Unknown	18	43			
Anaesthetist type						0.77
	Vet	16	58	1		
	Qualified Nurse	102	321	1.2	0.6 – 2.1	0.64
	Unqualified Nurse	57	176	1.2	0.6 – 2.2	0.62

*Odds ratios (OR) and 95% confidence intervals (CI) are reported for categorical data. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column.

7.3.1.2 Multivariable Model

Table 7.6 Final multivariable logistic regression model of the risk of anaesthetic-related death in Cats

Variable	Categories	β	s.e. β	OR*	95% CI*	P value
ASA grade	ASA 1-2					<0.001
	ASA 3					
	ASA 4 – 5					
	Trend+	1.16	0.23	3.2	2.0 – 5.0	
Urgency	Scheduled					0.04
	Urgent					
	Emergency					
	Trend+	0.46	0.23	1.6	1.0 – 2.5	
Intended Procedure	Minor			1		0.002
	Major	1.00	0.35	2.7	1.4 – 5.4	
Categorical Age	0- 0.5 years	-0.97	0.93	0.4	0.1 – 2.4	0.06
	0.5 – 5 years			1		
	5 – 12 years	0.51	0.29	1.7	0.9 – 3.0	
	12 years – max	0.73	0.32	2.1	1.1 – 3.9	
Categorical Weight	0-2 kg	2.75	0.85	15.7	2.9 – 83.6	0.002
	2-6 kg			1		
	6 - max	1.03	0.50	2.8	1.1 – 7.4	
	Unknown	0.11	0.81	1.1	0.2 – 5.5	
Endotracheal (ET) Intubation	No ET tube			1		0.06
	ET tube	0.66	0.33	1.9	1.0 – 3.7	
Pulse and pulse oximeter used	None			1		<0.001
	Pulse only	-1.10	0.34	0.3	0.2 – 0.6	
	Pulse oximeter only	-1.62	0.43	0.2	0.1 – 0.5	
	Pulse and pulse oximeter	-1.81	0.40	0.2	0.1 – 0.4	
Perioperative fluids	No fluids			1		<0.001
	IV Catheter only	-0.34	0.65	0.7	0.2 – 2.5	
	Fluids given	1.37	0.30	3.9	2.2 – 7.1	
Intercept		- 5.03	0.58			
Random Effect of Clinic Identity (rho)		0.08	0.02			0.05

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with corresponding Likelihood Ratio Test (LRT) P values. Number of observations 723 out of 730. +'Trend' represents the OR for a one-category increase in the variable.

In the multivariable model, health status as described by ASA grade, was retained as a major explanatory variable due to its low likelihood ratio test p value, its role as a confounder and its biological importance. A one-increment increase in patient health

status was associated with a 3.2-fold increase in odds (Table 7.6). Procedure urgency was retained in the model due to its low LRT p value and biological significance and an incremental increase in urgency was associated with a 1.6 fold increase in odds. Major intended procedures were nearly 3 times more likely to die than minor intended procedures. The odds associated with endotracheal intubation were 1.9.

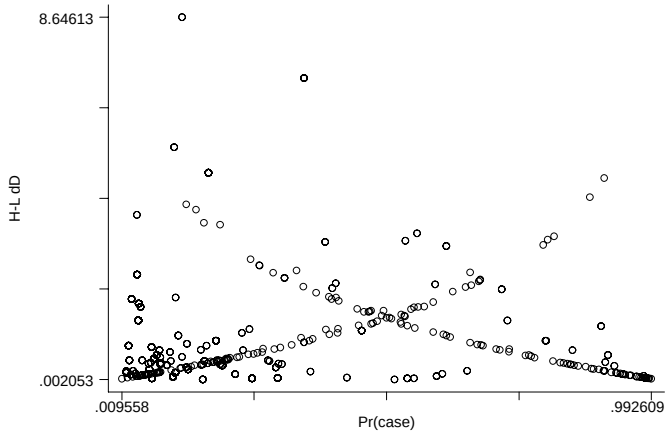
Age was retained in the model with a 2.1-fold increase in odds seen with older patients. Fractional polynomial analysis suggested best fit with a linear function (Royston, Ambler et al. 1999). However, the categorical version was preferred due to it having fewer missing values, as clinics were able to categorise but not state the exact age for twelve cats. Thought the P value for age was just above 0.05 (P=0.056), age was retained as it was considered biologically important and improved model fit. Pulse and pulse oximetry monitoring were both associated with a 4 to 5 fold reduction in odds. The use of perioperative fluids was associated with nearly 4 times increased odds of death. Categorical weight was retained in the model and, both low and high weight were associated with increased odds of death (OR=15.7 and OR=2.8, respectively). Endotracheal intubation was also just non-significant at the 5% level (P=0.06) and was retained in the model on biological grounds.

There was an interaction between the use of pulse oximetry and monitoring pulse, such that the magnitude in reduction of odds was less when the second method was used. The LRT was significant ($p<0.001$) and the two factors were combined as a single variable to reflect the interaction more clearly. Additionally, there was a tendency towards an interaction between intended procedure and endotracheal intubation such that the odds associated with endotracheal intubation was greater in the minor compared to the major procedure patients (endotracheal intubation OR=2.3 in minor procedures, OR= 0.6 in major procedures). However this was not significant (LRT p=0.08), the model fit was not as good when the interaction was included and thus it was not retained in the final model.

The addition of clinic identity as a random effect was significant (LRT P=0.054), indicating there was significant extra-binomial clustering of outcome at the clinic level (Hosmer and Lemeshow 2000), and this was retained in the final model. The within-clinic correlation described by rho was 0.08 (standard error 0.02). The goodness of fit as assessed by the Hosmer Lemeshow goodness-of-fit statistic was good (P = 0.90)

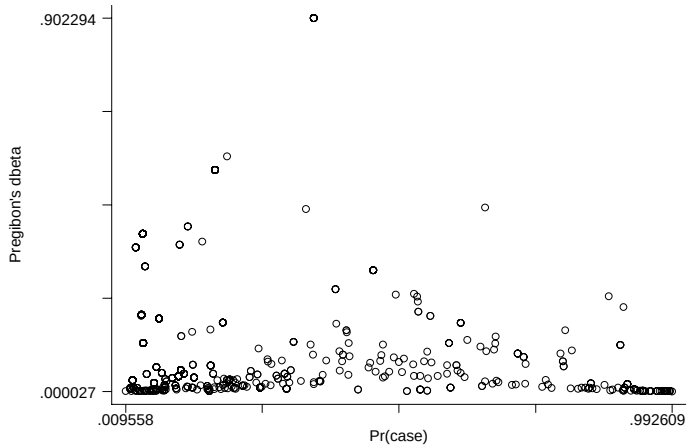
(Hosmer and Lemeshow 2000). The delta deviance diagnostic statistic also suggested good model fit with only 7 covariate patterns greater than 7.0 and none greater than 8.0 (Figure 7.1). Evaluation of the delta beta diagnostic statistic identified 7 covariate patterns with a delta beta greater than 0.8 and none greater than 1.0 (Figure 7.2). These observations were checked for errors and none found. When the model was run without these seven covariate patterns the parameter estimates were minimally changed. Hence these influential covariate patterns were retained in the model.

Figure 7.1 The Delta Deviance diagnostic statistic versus the estimated probability for the Cat model



*H-L dD, Hosmer-Lemeshow delta deviance diagnostic statistic. Pr(case), probability of being a case. J=264 covariate patterns.

Figure 7.2 The Delta Beta diagnostic statistic versus the estimated probability for the Cat Model



*Dbeta, Delta Beta diagnostic statistic. Pr(case), probability of being a case. J=264 covariate patterns.

7.3.2 Sick Cat Study

The mean age of controls in the sick population was 9.1 years (sd 5.3), 56% male and 44% female and 83% were neutered. Eighty-three percent of control sick cats were domestic shorthairs, 5% domestic longhairs and 11% pure breeds. Eighty-one percent were ASA grade 3, 19% ASA grade 4 or 5, and the presenting conditions were mostly cardiopulmonary, hepatic, renal, digestive, urogenital and endocrine disease (Table 7.7b). The majority had had bloods tests preoperatively ("Preoperative bloods", 53%), many had additional tests (42%), and most were starved (89%, Table 7.7b). In contrast to the general cat study population, the majority of sick cat procedures were urgent or emergency status (65%), and the mean duration of procedures was longer (Sick Cats 57.0 minutes (45.9sd), Cats 34.1 minutes (29.8 sd) p=<0.001).

Premedication was mostly undertaken with acepromazine combinations (49%), and infrequently with medetomidine (7%) or benzodiazepines and opioids (13%). Many cats did not receive premedication (31%, Table 7.7d). Induction of anaesthesia was primarily with propofol (67%), with thiopentone (10%), medetomidine combinations (8%), benzodiazepine and ketamine combinations (8%), mask inductions (4%), and Saffan (3%) less commonly used. Maintenance of anaesthesia was primarily with isoflurane (78%, Table 7.7d), and 83% had endotracheal tubes placed. Sixty-two percent of sick cats had an intravenous catheter placed and 53% received perioperative fluid therapy. Monitoring remained primarily of pulse rate (74%), respiration rate (90%), by stethoscope (51%), and with pulse oximetry (52%). Further intraoperative monitoring (ECG, capnography, blood pressure) was only seen in 10% of the sick controls.

7.3.2.1 Univariable Associations

Increased odds of anaesthetic-related death at the univariable level were associated with increasing weight, having other tests (not blood tests) undertaken perioperatively, increasing urgency, increasing procedure difficulty, major versus minor intended procedures, later induction times, controlled ventilation, fluid therapy, and poor recovery quality (Tables 7.6a-f). Reduced odds were associated with sedation versus general anaesthesia, the use of nitrous oxide as a carrier gas, monitoring pulse and pulse oximetry and monitoring the patient postoperatively.

Table 7.7.a The association of patient variables with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Categorical Age						0.22
	0- 0.5 years	4	2	2.2	0.4 – 13.2	0.39
	0.5 – 5 years	25	27	1		
	5 – 12 years	26	46	0.6	0.3 – 1.3	0.18
	12 years – max	38	38	1.1	0.5 – 2.2	0.83
Sex	Male	54	63	1		
	Female	40	50	0.9	0.5 – 1.6	0.81
Neutered	Entire	14	17	1		
	Neutered	76	94	1.0	0.5 – 2.1	0.96
	Unknown	4	2			
Categorical Weight						0.007
	0-3 kg	21	20	1.6	0.8 – 3.1	0.21
	3-6 kg	60	89	1		
	6 - max	12	3	5.9	1.5 – 22.8	0.003
	Unknown	1	1			
Overweight	Not overweight	75	100	1		
	Overweight	15	8	2.5	0.8 – 4.4	0.04
	Unknown	4	5			
Scales used	Scales	68	92	1		
	Estimate	24	20	1.6	0.8 – 3.2	0.15
	Unknown	2	1			
Breed						0.82
	DSH	70	94	1		
	DLH	9	6	0.9	0.5 – 1.8	0.77
	Persian	3	2	1.2	0.5 – 2.9	0.69
	Other Pure Breed	10	11	1.5	0.8 – 2.8	0.20
	Unknown		3			
Primary Case	Primary patient	84	102	1		
	Referral patient	10	10	1.2	0.5 – 3.1	0.68
	Unknown	0	1			
Previous Sedations or Anaesthetics within the month	None	74	87	1		
	One or more	15	19	0.9	0.4 – 2.0	0.84
	Unknown	5	7			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with the Likelihood Ratio Test (LRT) P values for multiple category variables at the top of 'P Value' column.

Table 7.7.b The association of patient variables with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Preoperative disease						0.13
	Cardiopulmonary	36	32	1		
	Neurological	2	5	0.4	0.1 – 2.0	0.22
	Digestive	27	35	0.7	0.3 – 1.4	0.29
	Urogenital	17	14	1.1	0.5 – 2.5	0.86
	Other	12	27	0.4	0.2 – 0.9	0.03
ASA grade (ASA4)	ASA 3	42	92	1		
	ASA 4-5	52	21	5.4	2.8 - 10.7	<0.001
Preoperative examination	No	2	1	1		
	Yes	92	112	0.4	0.0 – 4.6	0.46
Preoperative bloods	No	47	53	1		
	Yes	46	60	0.9	0.5 – 1.5	0.60
	Unknown	1	0			
Other tests	No	41	65	1		
	Yes	53	47	1.8	1.0 – 3.1	0.04
	Unknown	0	1			
	Adjusted ASA4**			1.1	0.6 – 2.0	0.90
Starved Preoperatively	No	6	7	1		
	Yes	78	101	0.9	0.4 – 1.1	0.86
	Unknown	10	5			
Water withheld	No	50	65	1		
	Yes	30	45	0.9	0.5 – 1.6	0.63
	Unknown	14	3			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column. **ORs are reported adjusted for health status (ASA4) when confounded by health status.

Table 7.7.c The association of procedural variables with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Urgency						0.03
	Scheduled	22	40	1		
	Urgent	50	60	1.5	0.8 – 2.9	0.20
	Emergency	22	13	3.1	1.3 – 7.5	0.01
	Trend**			1.7	1.1 – 2.6	0.01
Procedure Performed						0.02
	Neutering	1	0	1		
	Dental	10	20	1.5	0.5 – 4.4	0.46
	Diagnostics	9	27	1		
	Minor procedure	21	37	1.7	0.7 – 4.3	0.26
	Major procedure	40	29	4.1	1.6 – 10.6	0.001
	None	13	0			
Intended Procedure	Minor	48	84	1		
	Major	46	29	2.8	1.5 – 5.1	<0.001
Procedure Difficulty						0.02
	Simple	23	42	1		
	Moderate	34	56	1.1	0.6 – 2.2	0.76
	Difficult / V difficult	24	15	2.9	1.2 – 6.9	0.01
	No procedure	13	0			
Recumbency						0.50
	Lateral	23	30	1		
	Dorsal	33	31	1.4	0.7 – 2.9	0.38
	Sternal	7	14	0.7	0.2 – 1.9	0.43
	Multiple	30	38	1.0	0.5 – 2.1	0.94
	Unknown	1	0			
Duration						0.36
	0-29 min	31	27	1		
	30-59 min	27	44	0.5	0.3 – 1.1	0.08
	60-89 min	17	22	0.7	0.3 – 1.5	0.34
	90 –max	18	20	0.8	0.3 – 1.8	0.56
	unknown	1	0			
Duration intended						0.71
	0-29 min	19	27	1		
	30-59 min	33	44	1.1	0.5 – 2.2	0.87
	60-89 min	18	22	1.2	0.5 – 2.8	0.73
	90 –max	24	20	1.7	0.7 – 4.0	0.21
Induction Time						0.023
	8 am - 12 pm	39	65	1		
	12 pm - 5 pm	44	45	1.6	0.9 – 2.9	0.10
	5 pm – 8 am	9	3	5.0	1.2 – 20.5	0.01
	unknown	2	0			
	Trend**			1.9	1.2 – 3.0	0.01

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column. **'Trend' represents the OR for a one-category increase in the variable.

Table 7.7.d The association of anaesthetic agents with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
General Anaesthesia or Sedation	General Anaesthesia	89	98	1		
	Sedation	5	15	0.4	0.1 – 1.1	0.05
Premedication+						0.67
	None	31	35	1		
	Acepromazine	38	55	0.7	0.4 – 1.3	0.25
	Medetomidine	7	8	0.9	0.3 – 2.7	0.82
	BZ / Opioids only	14	15	0.9	0.4 – 2.2	0.88
Induction agents						0.28
	Thiopentone	11	11	1		
	Propofol	67	76	0.9	0.4 – 2.2	0.78
	Saffan	3	3	1.0	0.2 – 6.3	1.00
	Medetomidine combinations	3	9	0.3	0.1 –1.7	0.16
	Benzodiazepines / Ketamine	2	9	0.2	0 – 1.4	0.08
	Mask induction	6	4	1.5	0.3 – 7.0	0.61
	Other	2	1	2.0	0.1 – 27.2	0.60
Inhalation Agents						0.64
	Isoflurane	73	88	1		
	Halothane	3	5	0.7	0.2 – 3.1	0.66
	Sevoflurane	3	1	3.6	0.3 – 36.1	0.24
	None	15	19	1.0	0.5 – 2.0	0.90
Induction and Maintenance Combinations						0.89
	Injectable/Isoflurane	68	83	1		
	Injectable/Halothane	3	5	0.7	0.2 – 3.2	0.68
	Injectable/Sevoflurane	2	1	2.4	0.2 – 27.8	0.46
	Injectable Only	15	19	1.0	0.5 – 2.0	0.92
	Inhalational Only	6	5	1.5	0.4 – 5.0	0.54
Endotracheal (ET) Intubation	No ET tube	10	19	1		
	ET tube	84	94	1.7	0.7 – 3.9	0.20
Oxygen	No Oxygen	4	11	1		
	Oxygen	90	102	2.4	0.7 – 8.0	0.13
Nitrous oxide	No nitrous oxide	86	93	1		
	Nitrous oxide	6	20	0.3	0.1 – 0.8	0.02
Ventilation	Spontaneous	71	101	1		
	Controlled	23	11	3.0	1.3 – 6.6	0.005
	Unknown	0	1			
	Adjust ASA4**			1.6	0.7 – 3.6	0.23

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column. + Includes combinations of premedicant with other drugs (e.g. opioids). **ORs are adjusted for health status (ASA4) when confounded by health status.

Table 7.7.e The association of management and monitoring factors with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Perioperative fluids						<0.001
	No fluids	16	42	1		
	IV Catheter only	3	11	0.7	0.2 – 2.9	0.64
	Fluids given	75	60	3.3	1.6 – 6.6	<0.001
Monitoring person	Vet	17	15	1.0		
	Nurse	77	98	0.7	0.3 – 1.5	0.34
Other Duties of Monitoring Person						0.28
	No other duties	73	79	1		
	Performing the op	2	6	0.4	0.1 – 1.9	0.20
	Assisting the op	18	28	0.7	0.4 – 1.4	0.29
	Unknown	1	0			
Record	No record	45	67	1		
	Record	41	45	1.4	0.8 – 2.4	0.29
	Unknown	8	15			
Respiratory rate monitored	No respiratory rate	13	11	1		
	Respiratory rate	81	102	0.7	0.3 – 1.6	0.36
Pulse and pulse oximeter used						0.05
	None	23	13	1.0		
	Pulse only	27	41	0.4	0.2 – 0.9	0.02
	Pulse oximeter only	17	16	0.6	0.2 – 1.6	0.30
	Pulse and pulse oximeter	27	43	0.4	0.1 – 0.8	0.01
Stethoscope used	No Stethoscope	38	55	1		
	Stethoscope	56	58	1.4	0.8 – 2.4	0.23
Capnography used	No Capnograph	88	104	1		
	Capnograph	6	9	0.8	0.3 – 2.3	0.66
Arterial Blood Pressure	None	86	102	1		
	Indirect	8	10	0.9	0.4 – 2.5	0.91
	Unknown	0	1			
ECG	None	83	102	1		
	ECG	11	11	1.2	0.5 – 3.0	0.64

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category at the top of 'P Value' column.

Table 7.7.f The association of recovery and personnel factors with anaesthetic-related death in Sick Cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Recovery Quality	Good	15	79	1		
	Moderate / Poor	22	32	3.6	1.6 – 8.1	<0.001
	Unknown	18	2			
	Intraoperative death	39	0			
Recovery Observed	Continuously	31	42	1		
	5 minutes or more	16	68	0.3	0.2 – 0.7	0.001
	Unknown	8	3			
	Intraoperative death	39	0			
Postoperative Rectal Temperature Taken	No	37	88	1		
	Yes	18	23	1.8	0.9 – 3.9	0.09
	Unknown	0	2			
	Intraoperative death	39	0			
Veterinary surgeon familiarity with anaesthetic	Very Familiar	86	98	1		
	Familiar/Unfamiliar	7	11	0.7	0.3 – 2.0	0.53
	Unknown	1	4			
Veterinary surgeon type						0.08
	Senior Veterinarian	34	51	0.6	0.3 – 1.1	0.10
	Junior Veterinarian	58	54	1		
	Locum	2	7	0.3	0.1 – 1.4	0.09
	Other	0	1			
Veterinary surgeon Postgraduate qualifications						0.27
	None	64	73	1		
	Anaesthesia	5	13	0.4	0.1 – 1.3	0.13
	General	25	27	1.1	0.6 – 2.0	0.87
Anaesthetist Familiarity with Anaesthetic	Very familiar	73	82	1		
	Familiar/Unfamiliar	11	22	0.6	0.3 – 1.2	0.15
	Unknown	10	9			
Anaesthetist type						0.91
	Vet	13	15	1		
	Qualified Nurse	54	72	0.9	0.4 – 2.0	0.73
	Unqualified Nurse	27	26	1.2	0.5 – 3.0	0.70

*Odds ratios (OR) and 95% confidence intervals (CI) are reported for categorical data. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column.

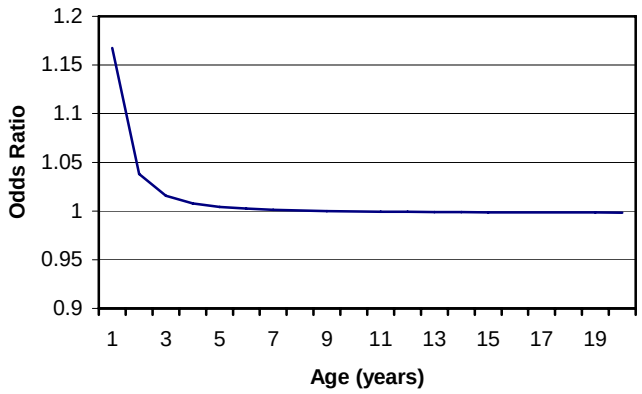
7.3.2.2. Multivariable Model

Table 7.8 The final logistic regression model of the risk of anaesthetic-related death in Sick Cats

Variable	Categories	β	s.e. β	OR*	95% CI*	LRT P value
ASA grade	ASA 3					
	ASA 4 – 5	2.04	0.48	7.7	3.0 – 19.9	<0.001
Perioperative fluids	No fluids			1		<0.001
	IV Catheter only	-1.74	1.15	0.2	0 – 1.7	
	Fluids given	2.10	0.63	8.2	2.4 – 28.0	
Nitrous oxide	No nitrous oxide			1		0.002
	Nitrous oxide	-1.99	0.72	0.1	0 – 0.6	
Pulse and pulse oximeter used	None			1		0.02
	Pulse only	-1.07	0.60	0.3	0.1 – 1.1	
	Pulse oximeter only	-0.75	0.75	0.5	0.1 – 2.0	
	Pulse and pulse oximeter	-2.06	0.71	0.1	0 – 0.5	
Categorical Weight	0- 6 kg			1		0.03
	6 - max	1.96	1.00	7.1	1.0 – 50.2	
Age (polynomial)	$(age)^{-2}$ – 1.274 Per year increase	0.0016	0.0012	1.001	0.999 – 1.004	0.04
Intercept		- 9.13	2.12			
Random Effect for Clinic Identity		Rho 0.22	Sigma 0.97			0.07

*Odds ratios (OR) and 95% confidence intervals (CI) are reported, with corresponding Likelihood Ratio Test (LRT) P values. Number of observations 203 out of 207.

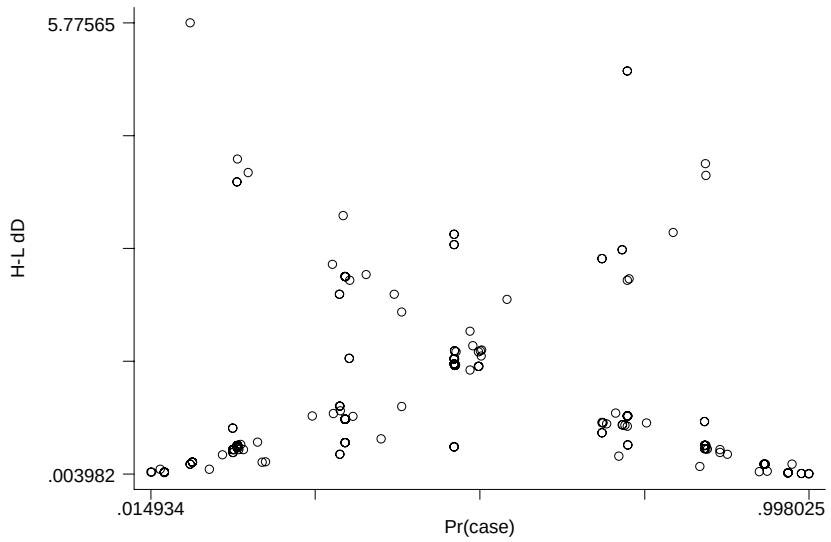
Figure 7.3 The association of anaesthetic-related death in Sick Cats with increasing age



In building the model for sick cats as in sick dogs, ASA grade remained an important variable on which to build the model, based on its likelihood ratio p value and biological significance. Increasing ASA grade was associated with a 7.7 fold increase in odds (Table 7.8). The use of fluid therapy perioperatively was associated with an odds ratio of 8.2 for patients receiving fluids. Nitrous oxide was associated with an odds ratio of 0.1, and pulse monitoring and pulse oximetry were also associated with a reduction in odds and retained in the model. The use of pulse monitoring was associated with an odds ratio of 0.3, pulse oximetry an odds ratio of 0.5, whilst using both monitors an odds ratio of 0.1. Patient weight was retained as the variable with patients 6kg or more, associated with a 7-fold increase in odds. Age, as a categorical factor, was not retained based on the LRT P value. However, the fractional polynomial version with a one-power term $((age)^{-2})$ remained significant at the multivariable level (Royston, Ambler et al. 1999). Increased odds were seen with low patient age in this variable when graphed (Figure 7.5). No significant interactions were found. Clustering at the clinic level was marginally significant in the mixed effects model (rho= 0.22, sigma = 0.97, P=0.072) and was retained in the model.

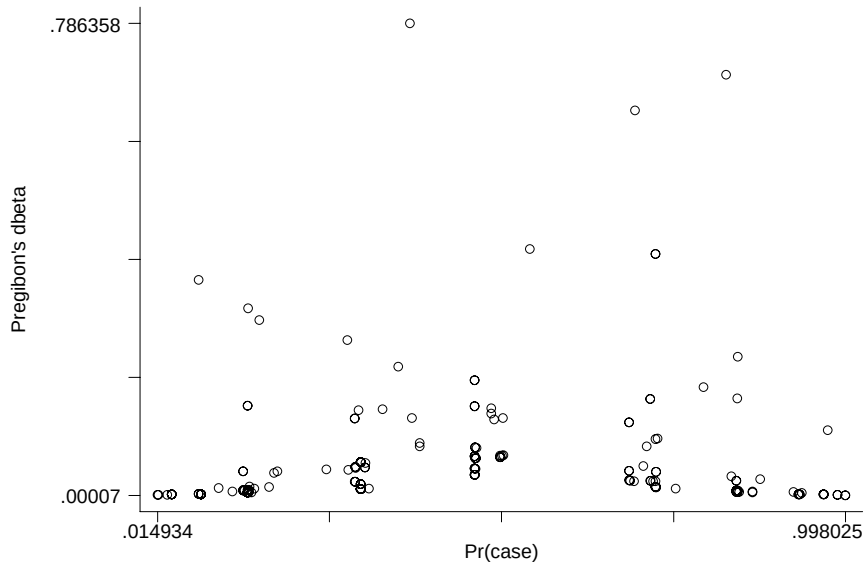
The model goodness-of-fit, as assessed by the Hosmer – Lemeshow statistic, was good (P value = 0.93) (Hosmer and Lemeshow 2000). Evaluation of the delta deviance diagnostic statistic (Figure 7.3) also supported good model fit, with only 4 covariate patterns greater than 4.0, and none greater than 6.0 (Hosmer and Lemeshow 2000). The delta beta diagnostic statistic identified 3 covariate patterns with a delta beta greater than 0.6 and none greater than 0.8 suggesting no major influential covariate patterns (Figure 7.4). The 3 marginally influential observations were checked for errors and none found. The model was rerun without these three covariate patterns, the parameter estimates were minimally affected and they were retained in the model.

Figure 7.4 The Delta Deviance diagnostic statistic versus the estimated probability for the Sick Cat Model



*H-L dD, Hosmer-Lemeshow delta deviance diagnostic statistic. Pr(case), probability of being a case. J=190 covariate patterns.

Figure 7.5 The Delta Beta diagnostic statistic versus the estimated probability for the Sick Cat Model



*Dbeta, Delta Beta diagnostic statistic. Pr(case), probability of being a case. J=190 covariate patterns.

7.4 Discussion

This chapter has identified a number of potential contributors to anaesthetic-related death in cats. Patient health status, age, weight, use of fluid therapy and patient monitoring of pulse and use of pulse oximetry were associated with outcome in both the Cat and Sick Cat studies. Additionally procedure urgency, intended procedure, endotracheal intubation were associated with anaesthetic death in the Cat study, and delivery of nitrous oxide was associated with anaesthetic death in the Sick Cat study. These factors may be useful in the assessment of patients risk and in reducing the odds of anaesthetic-related death.

7.4.1 Methodological Considerations

The importance of discussing the limitations of the method remains crucial and considerations of the method are broadly similar to those discussed in the last chapter in relation to risk factors in dogs (Chapter 6). Methodological issues specific to the cat studies and distinct from the dog studies will be considered in particular.

7.4.1.1 Study Design and Conduct

Case definition and selection were important considerations in evaluating the limitations of this study and are as discussed for dog risk factors in the last chapter (Chapter 6) (Hennekens and Buring 1987). The case definition and data checks were similar to those reported in the dogs and the independent review panel classified the cat cases against the same criteria as the dogs (Appendix 2.4). Considerations for the selection of the cases and controls were also similar to those in the dog study and the limitations of the assumed underlying population of Sick Cats were comparable. Specifically, the extrapolation from the overall cat distribution (i.e. the distribution in time and by clinic, derived from the cohort) to the sick population, may not have been an accurate representation of this population's distribution across the centres. However, without specific data on when the sick patients were anaesthetised during the study period (this was not recorded in the cohort), the data from the overall cat study cohort were the only data available. In the Cat study the ratio of 1:3 to 1:4 of case: control ratio was selected to maximise study power (Schlesselman 1982), in the Sick Cat study a compromise of 1:1 was accepted due to the concern of overloading individual clinics.

Issues of selection bias and non-response were comparable to those discussed in the dog study. The response rate for the cases was comparable to that of the dog study: of 248 deaths recorded in the cohort study, for only 14 deaths (6%) was there insufficient information to exclude them from being cases. The response rate for the controls was also good: 80% for the Cat Study (Dohoo, Martin et al. 2003) and the random sample of 20% of these non-responders did not indicate major differences in exposure histories from the returned controls and it would suggest the control population were not biased to a great extent by the failure to return these controls. The lower response rate of 59% in the Sick Cat compared to that of the Sick Dog study and remained a concern. The potential for bias due to the low response rate remained an important issue in interpreting the Sick Cat results. As in the dog study information on these Sick patient non-responders was difficult to identify and hence the extent and direction of any potential bias could not be quantified.

Information or observation bias was a concern, as for the dog study, and the same methods were adopted to minimise them (Breslow and Day 1980; Dohoo, Martin et al. 2003). Data entry errors were minimal also, and in random checks less than 5% of the cases and controls had an error. Misclassification of the outcome was reduced by appointing the independent review panel, and using a list of criteria to assess patients by (Chapter 2). Recall bias was minimised by requesting the controls soon after the anaesthetic was undertaken, such that both case and control questionnaires would have been completed in the immediate days after the event and the majority of the information required would have been recorded in the practices' patient records (Hennekens and Buring 1987; Dohoo, Martin et al. 2003). Hence efforts to minimize misclassification, particularly of a differential nature, were made as seen in the dog study.

7.4.1.2 Analysis

In the model building process, as in the dog study the likelihood ratio test statistic (LRT statistic) was preferred to the Wald test statistic when interpreting the significance of independent variables (Hauck and Donner 1977; Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003). The issue of missing covariate data was also a concern in this study (Breslow and Day 1980; Katz 1999). Efforts were made at the study conduct stage to minimise missing data in the cat study also, but some data remained unknown. At

the univariable level, separate categories for unknown values were created for categorical variables, allowing inclusion of this data and assessment of potential associations of the unknown categories with outcome. For patient weight, where a number of patients were of unknown weight (18 patients), an 'unknown' category was created rather than excluding these patients. That the odds of this unknown category were similar to the reference category and were not strongly associated with outcome (OR=1.1, 95% CI 0.2 – 5.5) supported this approach (Katz 1999).

In the multivariable model building process, independent variables with a large number of missing values were only considered in the multivariable analysis if they were of major biological importance. Again, postoperative temperature was incompletely recorded and was omitted from the multivariable analysis. Additionally, the approach of estimation of the value (Katz 1999) was employed for categorised age in the Cat study, when the actual age was unknown but the individual centres indicated a specific category of age. In the final model some variables were included with missing values, resulting in the deletion of these cases, though the number excluded was small (7 deleted patients in the Cat study and 4 in the Sick Cat study). As discussed in the dog study, the univariable factors were reported including all patients whilst the multivariable model was reported with the reduced dataset, as the datasets were unlikely to differ greatly due to the omission of these 7 and 4 patients respectively, and the missing values were spread over only a few variables (Breslow and Day 1980; Schlesselman 1982; Katz 1999).

The conceptual framework described in Chapter 2, helped direct model building as in dogs and rabbits and helped to avoid some numerical problems associated with logistic regression. As discussed in the Chapter 6, numerical problems include zero cells in contingency tables, covariates that completely separate the outcome groups, and collinearity of the data (Hosmer and Lemeshow 2000). The conceptual framework aided identification of potentially non-independent factors, whilst collapsing categories was employed where sparse data occurred. Concerns of confounding were addressed by measuring and adjusting for the anticipated variables in the multivariable analysis as discussed in the last chapter and similar confounders were seen in the cat study with health status remaining important (Breslow and Day 1980; Hennekens and Buring 1987; Dohoo, Martin et al. 2003).

Methods of assessing model fit were similar to those reported in Chapter 6 and suggested the models fit reasonably well for both cat studies. Large delta deviances greater than 4.0 to 5.0 are generally considered as poorly fitting covariate patterns (Hosmer and Lemeshow 2000), and though there were some covariate patterns greater than 5, there were only 7 greater than 7.0 (all less than 8.0) in the Cat model and only 4 greater than 4.0 (all less than 6.0) in the Sick Cat study. Similarly, there were no delta betas larger than 1.0 in the Cat or the Sick Cat models. Performing the analysis without the moderately influential covariate patterns did not affect the model coefficients, and hence it was concluded the models explained the data well (Hosmer and Lemeshow 2000; Dohoo, Martin et al. 2003).

Further validation of the models, as discussed in Chapter 6, could also have been performed here. As discussed in the last chapter, these methods of model validation are particularly important to models predicting prognosis or diagnosis of disease but are less relevant for studies identifying prognostic factors associated with an outcome whilst adjusting for confounders, such as the current study (Katz 1999; Dohoo, Martin et al. 2003). Hence in summary, though there remain limitations of the method adopted, generally these limitations were minor and the models explained the data well.

7.4.2 Descriptive Data

Data from the Controls provided further information on trends in anaesthesia to complement and support the clinic level data reported in Chapter 3. That acepromazine combinations were most commonly used was consistent with the clinic level data (Chapter 3), data in dogs (Chapter 6), and previous reports (Clarke and Hall 1990; Dyson and Pettifer 1997; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001). The predominance of propofol use for induction in anaesthesia was also consistent with the clinic level data (Chapter 3) and more recent work in the USA (Wagner and Hellyer 2000), but contrasts with earlier work in the UK and elsewhere (Clarke and Hall 1990; Dodman and Lamb 1992; Dyson, Maxie et al. 1998; Joubert 2000; Nicholson and Watson 2001). Interestingly medetomidine combinations were the next most commonly used agents, whilst significant minorities used Saffan (alphadolone / alphaxalone) and thiopentone. Maintenance of anaesthesia was primarily with isoflurane, indicating similar trends in anaesthetic use in cats and dogs and in the

USA and UK (Wagner and Hellyer 2000), though compared to the dogs (Chapter 6) more cats were maintained with injectable agents only (34%).

Patient monitoring remained limited in cats with observation of pulse and respiratory rates being the principle methods used. Encouragingly, separate personnel generally monitored the patient and pulse oximetry was used in just over half of the controls. Other methods of monitoring were used in less than 10% of the controls. As discussed in Chapter 6, this was comparable to recent veterinary practice-based work (Dyson and Pettifer 1997; Joubert 2000; Wagner and Hellyer 2000; Nicholson and Watson 2001), though contrasts with the more detailed medical requirements of the minimum monitoring standards published by Eichhorn and colleagues and recommended by the American Society of Anesthesiologists (1986).

7.4.3 Risk Factors in the Cat Study

Patient health status consistently was an important factor associated with anaesthetic-related death, with a 3.2-fold increase in odds seen with an increase of one category in patient status (ASA1-2, ASA3, ASA 4-5). The increased odds with poor health status were consistent with data from dogs and rabbits in the current study dogs (Chapter 5 and 6) and highlights the potential impact of pre-existing disease on patient outcome across species. Further, health status was important in the construction of the model (see conceptual framework, Chapter 2), as it was a major confounder to adjust for. The association with health status has been consistently reported in other veterinary studies (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004; Brodbelt, Hammond et al. 2005), and in human anaesthesia (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati, Ruzzi et al. 2004).

Urgency of the procedure was also an important factor to adjust other variables by in cats, and potentially was an important predictive factor for assessing patient

outcome. Increasing urgency by one increment (scheduled to urgent to emergency) was associated with a 1.6 fold increase in odds. Again, some of this effect could have resulted from residual confounding by health status. Increased risk has been associated with increasing urgency in the human and equine literature (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Pedersen, Eliasen et al. 1990; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). As discussed in Chapter 6 and as indicated in the conceptual framework (Chapter 2), procedural urgency was likely to reflect the ability to thoroughly assess and stabilise the patient preoperatively, as well as personnel staffing levels and personnel fatigue.

The association of increasing odds of anaesthetic-related death with increasing age, with cats 12 years or older being 2.1 times more likely to die than young cats, was an interesting finding. The increased odds with increasing age is consistent with the dog study results (Chapter 6), and work in a referral population of dogs, that demonstrated old age was associated with perioperative death (Hosgood and Scholl 1998). The increased odds seen in dogs in the current study was of a greater magnitude (Dogs 12 years or older, OR= 9.8) and though this may reflect species differences, the procedures were longer in dogs than cats (dogs duration 59.3 +/- 48.2min, cats duration 36.6 +/- 33.6 min, t test $p < 0.001$). An association with age may be more critical for longer procedures when potential physiological insults could be more prolonged. Work in a referral population of cats could find no association with age, though this may have reflected the lower power of that study (7 cases in a cohort of 138 cats) and again the tendency for shorter procedures in cats (cats median 88 minutes, dogs median 120 minutes) (Hosgood and Scholl 1998; Hosgood and Scholl 2002). Work in horses was consistent with an association with increasing age (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004), and in human anaesthesia the risk associated with increasing age has been well documented (Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al.

2001; Donati, Ruzzi et al. 2004). Biologically, as discussed in Chapter 6, old patients may be more susceptible to the depressant effects of anaesthetics, to hypothermia via impaired thermoregulatory mechanisms and to prolonged recoveries due to tendencies to reduced metabolic function and hypothermia (Waterman 1981; Dhupa 1995; Meyer 1999; Hall, Clarke et al. 2001).

Patient weight was also associated with anaesthetic-related death, with patients under 2 kg being nearly 16 times more likely to die and larger patients (6kg or more) nearly 3 times more likely to die than 2-6 kg patients. A component of this association with low weight could be due to residual confounding by age, such that a number of small patients were also younger. Nonetheless, the increased odds were consistent with the findings in dogs (Chapter 6) and were biologically plausible. Smaller patients could have been more prone to drug overdose, to hypothermia and to difficulties in perioperative management (e.g. intravenous catheter placement). It is interesting that larger patients were at increased odds, with a number of these classified as overweight. Obesity could contribute to perioperative complications due to the potential for respiratory compromise, lower cardiovascular reserves, and greater sink for inhalation agents to diffuse into in overweight patients (Hall, Clarke et al. 2001).

Intended procedure was retained in the final model with major procedure patients being three times more likely to die than minor procedure patients. This is consistent with the work seen in dogs and rabbits in the current study (Chapters 5 and 6), in equine anaesthesia (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). As discussed in Chapter 6, the procedural association was likely to reflect the increasing stress more complex and invasive procedures imposed on patient physiology. The difficulties of evaluating actual procedure, in relation to categorising patients that died prior to the procedure, were similar to those discussed in dogs. It was interesting that increasing duration of anaesthesia was not retained as factor in the final model, though there were univariable trends to increasing odds with increasing duration. This may reflect shorter procedures undertaken in cats compared to dogs, with any actual increased odds with increasing duration having been smaller in magnitude and as such not detected by this study

(Type 2 error) (Dohoo, Martin et al. 2003). Alternatively, it could be the result of the procedural effect including a large component of the duration effect.

Increased odds with endotracheal intubation have been reported before in cats (Clarke and Hall 1990; Dyson, Maxie et al. 1998). The cat airway is smaller and more sensitive to trauma, spasm and oedema than that of the dog and as such the process of intubation if poorly performed could be expected to increase complications (Hall and Taylor 1994; Hardie, Spodnick et al. 1999; Mitchell, McCarthy et al. 2000). The tendency to an interaction with intended procedure suggested that the increased odds were primarily seen in minor procedures, whilst in more major procedures there was a tendency to reduced odds with endotracheal intubation. Though not retained in the final model this interaction would suggest that in the more invasive procedures the advantage of securing an airway outweighed the risks of intubation, whilst in more simple procedures the process of intubation was more important.

The association with monitoring pulse and the use of pulse oximetry has not been reported in small animals and was not seen in the dog study (Chapter 6). Using a heart rate monitor was previously associated with increased odds of perioperative morbidity (Dyson, Maxie et al. 1998). Theoretical analysis in human anaesthesia suggested pulse oximetry alone would have detected 40 - 82% of reported perioperative incidents, combined with capnography 88 - 93% and with capnography and blood pressure 93% of incidents (Eichhorn, Cooper et al. 1986; Tinker, Dull et al. 1989; Webb, Van der Walt et al. 1993). That monitoring pulse and using a pulse oximeter were associated with reduced odds was encouraging, and suggests that some form of assessment of cardiovascular function (pulse quality and rate) and respiratory function (oxygen saturation) may be important in minimizing perioperative complications. That other methods of monitoring were not retained in the model was likely to reflect the limited power of the study to detect differences in rare exposures, as most other monitoring devices were used in less than 5% of the controls.

Finally, perioperative fluid therapy was retained in the model, with the administration of fluids being associated with nearly a four-fold increase in odds. This latter association was surprising and may reflect, at least in part, residual confounding by health status and duration of procedure. Nonetheless, a component of the increased odds may be related to the potential for fluid overload, increased cardiac preload and pulmonary

oedema. Cats, as a small species, would be more prone to fluid overdose and with very few practices measuring central venous pressure or using a fluid pump the potential for overdose was possible. This is an interesting association and further work is merited to assess the risks associated with fluid therapy.

No major drug associations were retained in the final model. Though univariable associations were seen, when adjusting primarily for health status, most associations were no longer significant. Premedication was not retained in the model, though there were tendencies to reduced odds (when premedication was included in the multivariable model) with acepromazine (adjusted OR=0.6, 95% CI 0.3 – 1.1), and benzodiazepines /opioids (adjusted OR = 0.5, 95% CI 0.2 – 1.4) compared to no premedication, whilst medetomidine premedication was associated with similar odds (adjusted OR= 1.1, 95% CI 0.3 – 3.4). The tendency to reduced odds with acepromazine is supported by previous work (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Johnston, Eastment et al. 2002; Brodbelt, Hammond et al. 2005), and the lack of increased odds with medetomidine contrasts to strong evidence associating xylazine (another $alpha_2$ agonist) with increased odds (Clarke and Hall 1990; Dyson, Maxie et al. 1998).

Similarly there were no clear associations with induction agent used. The perception in veterinary practice, that propofol is a 'safe' drug relative to other agents (Wagner, Wright et al. 2003; Bilborough 2005), was not observed here. Dose effects were evaluated for the major drugs used, and as reported in dogs, there were tendencies to reduced odds with increasing dose, though these were partly confounded by health status and had limited power given the small number of patients receiving specific drugs (Appendix 7.1). In contrast to the results reported in dogs (Chapter 6), there were no associations retained in the final model with maintenance / induction combinations either. This difference may reflect species differences, inability to detect real differences present in the cat study (type 2 error) or significance by chance (type 1 error) or bias in the dog study. Further work is warranted to evaluate the drug associations reported.

In summary, a number of factors have been identified associated with anaesthetic-related death in cats. Patient health status, age and weight, and procedure urgency and complexity may be useful in assessing patient risk preoperatively. The method of airway maintenance, pulse and pulse oximetry monitoring and perioperative fluid

therapy may influence outcome and these factors require further evaluation.

7.4.4 Risk Factors in the Sick Cat Study

Health status has consistently been identified as a major risk factor in this project with poor health status patients being at particular risk of anaesthetic-related death. In light of the Pilot study (see Chapter 2) and a retrospective case-control study undertaken in a referral population (Brodbelt, Hammond et al. 2005), it was identified that the overall study population would generate insufficient poor health-status control patients to be able to evaluate associations in this important subpopulation carefully. Additionally it was thought the potential for improving patient outcome was particularly great in this group if important associations were identified. Hence this sub-study was undertaken.

Poor health status remained an important factor to adjust for in the Sick Cat study, whilst urgency was not retained as a factor. That urgency of procedure was not a major factor reflects the trend to mostly urgent and emergency procedures in this poor-health status group. The increased odds for increasing ASA grade (ASA 5 versus ASA 3-4, OR=7.7), was greater than that of the overall Cat study (1 category increase, OR = 3.2) and a component of this difference in association with health status may reflect residual confounding by urgency of procedure in the Sick Cat study.

The association with low weight was not retained in this model. However, the increased odds with increased weight (OR= 7.1) were greater than the 2.8-fold increase in odds in the same 6 kg plus group in the Cat study. The greater magnitude reported in the sick population in part, may reflect a greater imprecision of sampling, given the smaller study size and the larger confidence interval (Dohoo, Martin et al. 2003). However, part of the increased odds with increasing weight could have been related to greater respiratory compromise, lower cardiovascular reserves, and a greater sink for inhalation agents to diffuse into, in larger and overweight patients (Hall, Clarke et al. 2001).

Age remained a significant variable associated with outcome in this high-risk group, though the magnitude of the association was small. Categorical age was not retained but a fractional polynomial version was, with a tendency to increased odds with low age being observed. The lack of a major association with increasing age was in contrast to

the association reported in the Cat study, and may reflect greater homogeneity of age within this higher risk group.

The association with administering fluid therapy, observed in the Cat study, was retained in the Sick Cat study, though the odds ratios reported were more extreme (Sick Cat study OR = 8.2, for receiving fluids, Cat study OR=3.9). The greater odds observed with perioperative fluids may reflect less confidence in the actual odds ratio. Additionally, these more extreme coefficients may reflect cats less able to accommodate large volumes of fluids, and potentially greater benefits in securing intravenous access (Hall and Taylor 1994).

Monitoring of pulse and pulse oximetry remained associated with outcome in the sick cat group, and the magnitude of reduced odds with pulse and pulse oximetry were comparable to those reported in the Cat study. That patient monitoring was still relevant in the higher risk group could be expected, given these patients would be particularly sensitive to cardiovascular and respiratory disturbance (Hall, Clarke et al. 2001). Finally, the observation that administering nitrous oxide was associated with reduced odds of anaesthetic-related death, was an interesting finding, and co-administration of nitrous oxide can reduce the other inhaled anaesthetic agent requirements and reduce dose-dependent cardiopulmonary depression of this other agent (Steffey, Gillespie et al. 1975; Hall, Clarke et al. 2001). This association has not been reported previously and merits further evaluation.

In summary, the associations identified in this poor health status subpopulation were similar to many of those reported in the overall Cat study. In these sick cats, patient health status remained an important factor to aid patient assessment, as was weight, and to a lesser extent age. The use of pulse and pulse oximeter monitoring remained associated with outcome and may be valuable in reducing the odds of anaesthetic-related death in sick patients. Fluid therapy appeared detrimental to patient outcome whilst nitrous oxide was associated with reduced odds and both these observations warrant further evaluation.

7.4.5 Causation and Association

The step from association to causation is difficult to establish in an observational study as discussed in Chapter 6 (Schlesselman 1982). Hill (1965) described a number of criteria against which to assess the likely role of observed factors in the causation of an outcome. The strength of the association, the consistency with other work, the specificity of the association, temporality of the relationship, the presence of a biological gradient, the biological plausibility, the coherence with the known biology of the disease or subject under study, the presence of supporting experimental evidence, and the presence of analogy to a similar condition are all criteria to base an assessment of the likely role of an association in causation (Hill 1965).

Based on these criteria patient health status and in view of the conceptual framework developed (Chapter 2), procedure urgency and complexity, patient age and endotracheal intubation would appear to causally contribute to anaesthetic-related death. Patient health status has been consistently reported throughout this study in a number of species and in previously published work (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Clarke and Hall 1990; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Hosgood and Scholl 2002; Donati, Ruzzi et al. 2004; Johnston, Eastment et al. 2004; Brodbelt, Hammond et al. 2005), the association was found to be reasonably strong (OR=3.2), there was temporality of patient disease and subsequent outcome, there was a biological gradient (increasing odds with increasingly poor status), and the results were plausible and coherent with current knowledge.

Similarly, the association with urgency of the procedure has been reported across species in the current study and in previous work (Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Pedersen, Eliasen et al. 1990; Johnston, Taylor et al. 1995; Biboulet, Aubus et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). The magnitude of the association, though not as large as seen for

health status was still biologically significant (OR=1.6 for trend), and again there was a biological gradient for increased odds with increasing urgency, and there was appropriate temporality of urgency and outcome. The association was plausible and coherent with current understanding of anaesthesia and the risks associated with poor patient stabilisation prior to anaesthesia (Hall, Clarke et al. 2001) and as such it would appear procedure urgency contributed to anaesthetic-related death.

The complexity of the procedure would appear also to contribute to anaesthetic-related death. This finding was demonstrated across species in the current study, and in previous work in equine anaesthesia (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Farrow, Fowkes et al. 1982; Fowkes, Lunn et al. 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Newland, Ellis et al. 2002; Donati, Ruzzi et al. 2004). The association was strong in cats (OR= 2.7), it was plausible, temporal and coherent with the current understanding of the physiological impact of surgery on anaesthesia (Clarke 1970; Hall, Young et al. 1978; Kehlet 1984). The comments in dogs and rabbits in relation to intended and actual procedure would equally apply here, and the measured association reflected both actual procedure in part and also anticipated procedure and the type of patient based on that element.

The association with age was consistent with work in other species (Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Johnston, Taylor et al. 1995; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Hosgood and Scholl 1998; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2002; Donati, Ruzzi et al. 2004; Johnston, Eastment et al. 2004). There was a strong association in cats 12 years and older (OR=2.1), age exhibited a gradient of odds with increasing age, the association was plausible and it was consistent with the understanding of the physiological changes with age (Thurmon, Tranquilli et al. 1996). Hence, increasing age appears to causally contribute to the outcome.

Increasing odds with endotracheal intubation have been reported before in cats (Clarke and Hall 1990; Dyson, Maxie et al. 1998), and the odds reported were of a

reasonable magnitude (OR=1.9). No biological gradient was possible given only mortality was studied, however the results are plausible and coherent with the perceived knowledge of the technical considerations for intubation in cats (Hall and Taylor 1994). The tendency to an interaction with procedure type as discussed earlier would support the causal link, and on balance the evidence supports a causal association of intubation with anaesthetic-related death. The decision to intubate a specific cat should be based on the risks of the technique versus the need to secure a patent airway.

Other factors observed in the Cat and Sick Cat studies require further evaluation before concluding they causally contribute to anaesthetic-related death. These other associations were not based on *a priori* hypotheses, may not have fitted entirely within the conceptual framework and data-derived hypotheses should be interpreted cautiously (Hennekens and Buring 1987). The magnitude of the association with weight was large in the Cat study, and increased odds associated with extremes of weight were consistent with work in dogs in the current study. However, previous work has not demonstrated a weight-related risk in cats and an element of the magnitude of the odds reported with low weight could represent residual confounding by age, due to neonatal considerations. A gradient of increasing risk with increasing weight was not demonstrated, and though plausible and coherent with current understanding specifically of hypothermia in small patients (Waterman 1981; Dhupa 1995; Meyer 1999; Hall, Clarke et al. 2001), further work is merited before concluding that weight causally contributed to the outcome.

Monitoring pulse and the use of pulse oximetry were associated with reduced odds in both the Cat and the Sick Cat studies, and though interesting and the results were of a reasonably large magnitude (OR=0.2 -0.3), this was not demonstrated in other species in the current study or in previous work. In human anaesthesia there is work that suggests pulse oximetry was associated with reducing complications (Eichhorn, Cooper et al. 1986; Tinker, Dull et al. 1989; Webb, Van der Walt et al. 1993) and the findings are plausible, however further work is merited before the causal link is concluded. Similarly, the finding that fluid therapy was associated with increased odds requires further evaluation. The association was strong (OR= 3.9 in the cat study, OR=8.2 in the sick cat study), and this increasing odds in sicker patients lends a biological gradient to the evidence. However, though plausible if fluid overload was occurring, as indicated in the conceptual framework (Chapter 2), fluid therapy may have in part also reflected

the procedure undertaken and patient health status, and residual confounding may account for much of this association. Until further work supports this finding, it should be viewed cautiously. Finally the association with nitrous oxide in the Sick Cat study was also interesting, though has not been reported in previous work. Again, it is biologically plausible (Steffey, Gillespie et al. 1974; Steffey, Gillespie et al. 1975), but further work is merited to evaluate the association more carefully.

In summary, a number of factors were identified as potential contributors to the multi-factorial process of anaesthetic-related death in cats. Severity of preoperative disease, procedural urgency and complexity, and age formed a useful core of variables to aid patient risk assessment preoperatively. Extremes of patient weight were associated with increased odds and may assist patient assessment. Modifiable factors included endotracheal intubation which was associated with increased odds, should be undertaken carefully and may be appropriate to avoid in certain circumstances. Monitoring methods, the use of perioperative fluids, and the administration of nitrous oxide may additionally modify risk and merit further investigation.

Chapter 8: General Conclusions

This study has described the current risks of anaesthetic-related mortality in small animals within a large cohort of small animal practices and has identified risk factors associated with this outcome in the three most commonly anaesthetised small animals: dogs, cats and rabbits. The aims of this study were to estimate risks of anaesthetic-related death, to identify risk factors associated with anaesthetic-related death and to make recommendations to veterinary practitioners to improve the clinical practice of small animal anaesthesia.

A convenience sample of motivated and interested practices was chosen over a random sample due to the amount of data requested, the long data recording period and the need for good practice compliance. Though care should be taken in extending these conclusions to all UK small animal practices as less interested, non-involved practices could have substantially different practices and complication rates, the conclusions drawn from this sample were valid for this cohort. Given the large sample size and involvement of approximately 0.5% of UK practices, the range of practice types involved in the study, and the similar characteristics of practice size and type when compared to data from the RCVS (RCVS 2000; RCVS 2004), the results are likely to be relevant, if not directly applicable, to most UK small animal veterinary practices.

The case definition of perioperative death (including euthanasia) occurring after premedication and within 48 hours of termination of the procedure, except where death or euthanasia was due solely to inoperable surgical or pre-existing medical conditions, inevitably allowed some degree of subjectivity and included a spectrum of causes of death. The consistency of case classification based on this definition and the reduction of subjectivity were increased by appointing an independent review panel to classify all cases in dogs and cats against an explicit set of criteria (Appendix 2.4). The deaths included within this definition were restricted, based on the criteria, to those in which it was not reasonable to exclude anaesthesia from having contributed to the outcome. This approach reduced the potential for misclassification bias.

The nested case-control study design was particularly appropriate for the identification of risk factors, given the rare nature of anaesthetic-related death in the species studied (Schlesselman 1982; Hennekens and Buring 1987; Dohoo, Martin et al. 2003). A

cohort design alone would have been inefficient and practically difficult, requiring the recording of large amounts of information for every patient. The selection of the controls for this study however was particularly important, to ensure that they were representative of the population from which the cases were derived (Schlesselman 1982). The use of the nested case-control approach and randomly and prospectively selecting the dog and cat controls from the underlying cohort reduced selection bias in the controls selected and thus increased the validity of any conclusions drawn.

The description of practice trends of this large cohort provided a valuable insight into the current practice of small animal anaesthesia in the UK. Since the last UK study (Clarke and Hall 1990), new drugs have been introduced including medetomidine, propofol, isoflurane and sevoflurane, and pulse oximetry has been widely adopted for perioperative patient monitoring. However, preoperative patient workup and evaluation remains limited, other methods of electronic patient monitoring are rarely used and perioperative fluid therapy is infrequently given.

The risk of anaesthetic-related death in the study population of cats and dogs was approximately half of that published in the previous UK study when reported by health status (Clarke and Hall 1990). The overall risks of 0.17% and 0.24% in dogs and cats respectively, were a reduction compared to risks reported in the last UK study, and are broadly comparable to other international small studies (Dodman and Lamb 1992; Rintasalo and Vainio 1995; Dyson, Maxie et al. 1998; Joubert 2000). Given the relatively highly qualified population of veterinarians participating in the study compared to the level of qualifications documented by the RCVS in the UK (RCVS 2000), this estimate is likely to be an overestimate of the risk in the UK. From a comparisons perspective this is likely to have been the case in the other studies also, that is the most motivated practices and potentially the safest participate in such studies. Nonetheless, when compared to approximately 0.02 to 0.005% for similarly defined anaesthetic-related death in man (Tikkanen and Hovi-Viander 1995; Eagle and Davis 1997; Suan, Perez-Torres et al. 1997; Biboulet, Aubus et al. 2001; Kawashima, Seo et al. 2001), it is clear there remains substantial room for improvement. Further, the greater than ten-fold increase in risk for sick dogs, cats and rabbits (1.33%, 1.40% and 7.37% respectively), compared to healthy patients (0.05%, 0.11% and 0.73% respectively), identified high-risk patients as a population in which major reductions

in risk should be made. Patient health status was an important risk factor that has been consistently reported in other small animal studies (Clarke and Hall 1990; Dyson, Maxie et al. 1998; Hosgood and Scholl 1998; Brodbelt, Hammond et al. 2005), in horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004) and in human anaesthesia (Marx, Mateo et al. 1973; Hovi-Viander 1980; Lunn and Mushin 1982; Pottecher, Tiret et al. 1984; Tiret, Desmonts et al. 1986; Buck, Devlin et al. 1988; Cohen, Duncan et al. 1988; Forrest, Cahalan et al. 1990; 1990; Pedersen, Eliasen et al. 1990; Forrest, Rehder et al. 1992; Pedersen 1994; Warden, Borton et al. 1994; Tikkanen and Hovi-Viander 1995; McKenzie 1996; Warden and Horan 1996; Wolters, Wolf et al. 1996; Biboulet, Aubus et al. 2001; Morita, Kawashima et al. 2001; Donati, Ruzzi et al. 2004).

It was interesting that the majority of these anaesthetic-related deaths occurred postoperatively. Of the postoperative deaths in dogs, cats and rabbits, 50% occurred within 3 hours of termination of anaesthesia. Increased awareness of the risks of the postoperative period is merited and improvements in the monitoring and management of patients, particularly in the early postoperative period, could reduce complications substantially.

The species-specific mortality risks in other small animals have not been previously documented. The risks of greater than 1% in most species were high and work must be done to improve the anaesthetic management of these species. Rabbits in particular, merit close attention as they are relatively commonly anaesthetised, but still carry a high risk of anaesthetic-related death. The major risk factor for anaesthetic-related death in rabbits was patient health status. Additionally, increasing procedure complexity (major versus minor), increasing duration of anaesthesia and increasing veterinary surgeon familiarity with the anaesthetic-agents used were also associated with death. Identifying potentially high-risk patients, based on their health status, the procedure to be undertaken and the intended duration of anaesthesia, would be valuable in quantifying the risks of anaesthesia and targeting patients that require intensive perioperative management. In a species that is still only infrequently anaesthetised in many practices, the veterinarians' familiarity with the anaesthetic used was more important than the specific drugs used. However, matching by clinic identity in this section of the study limited the ability to look closely at drug factors in rabbits as many centres used

only one protocol for rabbits. Further work will be required to address specific drug-related associations, but in the absence of this work the use of drugs familiar to the clinician is to be highly recommended.

Health status was found to be a consistent and important risk factor throughout this study in the three species examined in detail and this work supports the validity of applying the ASA grade system to veterinary species. It was a valuable predictor independent of patient size and age, with the latter variables often being retained as separate factors within the same models. The stratification of ASA grade into 3 categories in dogs and cats represented the major degrees of pre-existing pathology, with stratification into minor or no disease (ASA grade 1-2), severe non-incapacitating disease (ASA grade 3), and life threatening disease (ASA grade 4-5) and from a biological perspective represented the major divisions of risk by health status. However, just as the binary division (ASA grade 1-2 versus 3-5) used in rabbits may have insufficiently accounted for divisions in disease severity, the 3 category stratification may also have incompletely represented disease severity. Potentially a four category finer stratification could have been adopted (ASA 1, 2, 3, 4-5) allowing more precise modelling of disease risk. Interactions by health status were also explored. At the univariable stage, in dogs there were non-significant tendencies for greater effects seen with age and intended duration in the healthy patients, than the sick patients. In cats, evidence of interaction was observed for age, intended procedure and fluid therapy, such that healthy patients had greater odds with increasing age, whilst the associations with major intended procedure and fluid therapy were greater in the healthy patients. These interactions were not significant and not retained in the final models. However, an alternative approach would have been to explore models in healthy patients only (as was performed for sick patients) to account for this potential heterogeneity. Nonetheless, health status as described was strongly associated with outcome and an important confounder when building the model.

Increasing patient age and low patient weight were also associated with anaesthetic-related death and careful consideration of the risks of anaesthesia and preoperative patient preparation would be particularly important in the sick, old and small dog. Procedural urgency, complexity (major versus minor) and intended duration were procedural factors associated with outcome and should also be considered when

planning the procedure to be undertaken and the perioperative management of the patient. The induction and maintenance combination was associated with outcome and was the major modifiable factor identified in dogs. Mask induction of anaesthesia was associated with a 6-fold increase in odds as was halothane maintenance compared to isoflurane. The increased odds associated with total inhalational anaesthesia are consistent with previous work in small animals and horses, in which mask inductions have tended to be associated with increased risk of complications (Clarke and Hall 1990; Johnston, Taylor et al. 1995; Dyson, Maxie et al. 1998; Johnston, Eastment et al. 2002); re-evaluation of this method is recommended. Increased odds of anaesthetic-related death with halothane anaesthesia, compared to isoflurane, have not been demonstrated in small animals, and halothane maintenance was not significantly different to isoflurane in a randomised controlled trial of horses (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004). However, isoflurane was associated with reduced odds compared to halothane in young horses in this study (Eastment, Johnston et al. 2002; Johnston, Eastment et al. 2004). Isoflurane causes less myocardial depression, greater vasodilatation, and sensitises the heart less to catecholamine-induced arrhythmias than halothane, potentially reducing afterload on the heart and work of the heart (Joas and Stevens 1971; Steffey, Gillespie et al. 1975; Steffey and Howland 1977; Hellebrekers 1986; Tranquilli, Thurmon et al. 1988; Grandy, Hodgson et al. 1989; Lemke, Tranquilli et al. 1993; Hikasa, Okabe et al. 1996; Hikasa, Ohe et al. 1997; Hodgson, Dunlop et al. 1998) and as such could be associated with reduced odds. Further work is merited to evaluate the risks associated with isoflurane.

High-risk dogs were investigated separately in the sub-population of sick patients anaesthetised in the study. Health status, procedure urgency and complexity (major versus minor) and patient weight were significant factors retained in the Sick Dog model and would be valuable to aid assessment of these patients. Halothane was associated with a 5-fold increase in odds compared to isoflurane and the use of isoflurane over halothane should be considered in these patients. Additionally, preoperative blood testing, particularly in the most sick patients (ASA 4-5) was associated with reduced odds, as was spontaneous ventilation versus controlled ventilation. Both these observations were not based on *a priori* hypotheses and have not been reported previously, and so should be interpreted cautiously. However, preoperative bloods on their own or as a marker for further preoperative patient

workup, may allow better assessment of these sick patients and encourage appropriate patient management. Few dogs are routinely ventilated for procedures other than for thoracic surgery which may carry an inherently higher risk, or when ventilation has been poorly maintained spontaneously and residual confounding may thus underlie this association. The findings in the Sick dog study proved interesting but given the high non-response rate in the controls, must be treated cautiously.

The increased odds associated with increasing poor health status was of a similar magnitude in cats and dogs (OR= 3.2 for a 1 category increase in ASA grade, dogs OR = 2.9). Urgency of procedure and procedural complexity (major versus minor) were also associated with death and should be considered when assessing anaesthetic risk in cats. Extremes of weight and increasing age were associated with increased odds and again patient health status, age and weight should be major factors used to assess the patient risk. Endotracheal intubation was associated with increased odds, in contrast to the results in dogs. This is consistent with previous work (Dyson, Maxie et al. 1998) and suggests greater care should be taken with endotracheal intubation in cats. Interestingly, no drug related factors were identified, but patient pulse monitoring and pulse oximetry were associated with reduced odds. This has not been documented before in small animals, but is consistent with work in man (Eichhorn, Cooper et al. 1986; Tinker, Dull et al. 1989; Webb, Van der Walt et al. 1993). Based on these findings, regular monitoring of pulse and the use of pulse oximetry should be recommended. Whether these are the only methods required is uncertain, as other methods, such as capnography and measurement of blood pressure, were infrequently used and hence difficult to assess in this study. Perioperative fluid therapy was associated with increased odds. This finding has not been documented previously, though inadvertent fluid overload would be easier to achieve in cats than dogs given their smaller size. However, the finding may be the result of residual confounding by health status, procedure length or complexity and as such requires further evaluation.

Within the sick sub-population of cats studied, similar factors to those reported in the Cat Study were identified, with the addition of nitrous oxide being associated with reduced odds. Nitrous oxide does reduce the inhalation agent requirements of other inhalation agents co-administered (DeYoung and Sawyer 1980) and as such may reduce dose-dependent cardiovascular and respiratory depression. This finding merits

further work and again caution should be exercised with these results given the large non-response rate for the controls

In conclusion, risks of anaesthetic-related death in small animals remain substantially higher than that reported in man, dogs and cats and major risk factors for anaesthetic-related death have been identified in dogs, cats and rabbits. Less commonly anaesthetised small animal species were at greatest risk. Given the need to anaesthetise rabbits more often than other minor small animal species and the high risk of death, rabbits should be targeted as a species requiring immediate improvement in anaesthetic management. Particular attention to patient management for the poor health status patients is warranted and closer attention to the immediate postoperative period may reduce the risk of death. Other patient factors: age and weight and procedure factors: complexity, duration and urgency were consistently more important than drug factors in the species studied, though the use of isoflurane may be advantageous over halothane and monitoring of patient pulse and the use of pulse oximetry should be recommended. Good anaesthetic practice, combined with the results of experimental work and the factors highlighted in this study should be used to improve anaesthetic management of small animals and reduce the risk of anaesthetic-related death.

Appendices

Appendix 2.1 American Society of Anesthesiologists Health Status Classification

Class 1 – fit and healthy, no systemic disease.

Class 2 – mild to moderate systemic disease only.

E.g. skin tumour, chronic arthritis, fracture without shock.

Class 3 – severe systemic disease, causing mild symptoms / limiting activity, but not incapacitating.

E.g. moderate hypovolaemia, anaemia or pyrexia, mild to moderate heart failure.

Class 4 – severe systemic disease that is a constant threat to life.

E.g. severe uraemia, toxaemia, hypovolaemia, heart failure.

Class 5 – moribund patient that is not expected to survive 24 hours with or without the operation.

E.g. extreme sepsis / shock.

(Anon 1963)

Appendix 2.2 CEPSAF Case Diary Questionnaire

CEPSAF Case Diary

Sheet No: _____ Clinic No: _____

Branch Initials (if more than one branch): _____

ALL anaesthetics and sedations of dogs, cats and exotic species should be entered on this form.

Date	Patient name or ID	Species: Dog (D), Cat (C) or Exotic Species *(please specify)*	Sedation (Sed) or Anaesthetic (An)	Outcome at 48 hours: Alive (A), Dead (D)* or Euthanased (PTS)*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				

*For patients that die or are euthanased please also indicate the cause of death or reason for euthanasia in 'Outcome at 48 hours', e.g. inoperable tumour, anaesthetic related, etc.

Please return to: Dave Brodbelt, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU, Fax 01638 555 659

Explanatory Notes for the Case Diary:

1. Date – this refers to date of administration of the anaesthetic or sedation.

2. Patient name or identification – this column is to allow you to identify the patient.

3. Species – please indicate whether the animal was a dog, cat or an exotic species. If an exotic pet please specify the species, e.g. rat, mouse, rabbit, parrot, tortoise etc.

4. Sedation or Anaesthesia – For the purpose of this study, sedation and anaesthesia are defined as below:

    a. Sedation = Chemical restraint not inducing complete unconsciousness. Endotracheal intubation would not be possible.

    b. General anaesthesia = Complete unconsciousness results, allowing endotracheal intubation if desired.

5. Outcome at 48 hours – The outcome at 48 hours after the end of the procedure of ALL patients should be recorded in this column. There are three possible outcomes defined as:

    a. Alive – All patients that remain alive for at least 48 hours after the end of the procedure.

    b. Dead – All patients that die within 48 hours of the end of the procedure.

    c. Euthanased / PTS – All patients that are euthanased within 48 hours of the end of the procedure.

Please now complete a CASE-CONTROL QUESTIONNAIRE, for all DOGS, CATS and EXOTICS that DIE or are EUTHANASED UNLESS:

1. They DIED or were EUTHANASED due to surgical causes, inoperable surgical or pre-existing medical conditions, **where anaesthesia or sedation did not contribute to the death or decision to euthanase.**

2. They remained ALIVE at 48 hours after termination of the procedure.

An example of euthanasia for an inoperable surgical condition would include a patient euthanased during surgery due to the presence of abdominal tumours. An example of a patient that died as a result of surgery would include the patient that undergoes bowel resection and anastomosis and dies following intestinal anastamosis dehiscence postoperatively.

If you are in any doubt as to whether to complete a case-control questionnaire for an animal that dies or is euthanased or for any other reason, please contact **Dave Brodbelt** at direct line 01638 555651, Mobile 0775 950 4135, or email dave.brodbelt@aht.org.uk.

Appendix 2.3 CEPSAF Case-Control Questionnaire

CEPSAF

Confidential enquiry into perioperative small animal fatalities

Case control questionnaire

Clinic number ☐

Instructions

1. This form must be filled in for ALL perioperative DEATHS (including patients euthanased) within 48 hours of termination of the procedure EXCEPT for:

   Patients that DIED or were EUTHANASED for inoperable surgical or pre-existing medical conditions, where anaesthesia or sedation did not contribute to the death or decision to euthanase.

   If you are uncertain as to whether or not to complete this form please consult the decision tree at the beginnning of your CEPSAF Folder or contact Dave Brodbelt at the AHT as below.
2. Please also complete this form for DOG and CAT CONTROLS. When completing this questionnaire for a control please do not complete page 8 (Section H : Fatality Details).
3. All information provided will be **kept strictly confidential.**
4. Please answer all questions unless directed not to. Questions require either ticking a box of the appropriate choice or responding with a written answer. If you do not know the answer to a question please write 'unknown' next to the question.
5. Please add any further comments that you think might be helpful at the end of the questionnaire.
6. If you have any questions please contact **Dave Brodbelt at: Tel 01638 555651, Fax 01638 555659, mobile 0775 950 4135, email dave.brodbelt@aht.org.uk.**

When completed please return in the enclosed reply paid envelope, to:

Dave Brodbelt
CEPSAF
Animal Health Trust
Lanwades Park, Kentford
Newmarket, Suffolk CB8 7UU

Section A: Patient's details

1. Patient name or other form of ID: ☐
2. Please state the patient's species: ☐ DOG ☐ CAT Exotic (please specify species) ☐
3. What was the patient's BREED? ☐
4. Please state the sex of patient: ☐ Male ☐ Female ☐ Not known
   ☐ Entire ☐ Neutered ☐ Not known
5. What was the patient's age? ☐ years ☐ months
6. What was the patient's weight? ☐ kg
   a) How was the patient's weight assessed? ☐ Scales ☐ Estimate
   b) In your opinion was the patient overweight? ☐ YES ☐ NO
7. What type of case was this? ☐ Primary ☐ Referred
8. Did the patient have any other GENERAL ANAESTHESICS in the last month? ☐ YES ☐ NO ☐ Not known
   If YES, please specify the number of GA's: ☐ 1 ☐ 2 ☐ 3 or more ☐ Not known
9. Did the patient have any other SEDATIONS in the last month? ☐ YES ☐ NO ☐ Not known
   If YES, please specify the number of sedations: ☐ 1 ☐ 2 ☐ 3 or more ☐ Not known

Section B: Pre-operative evaluation

Now we are interested in aspects related to the evaluation of the patient prior to the procedure.

10. Preoperatively were there any ongoing medical conditions (eg heart failure, renal disease, etc)?

☐ YES ☐ NO ☐ Not known If NO, please go to **Q11**

If YES, please specify the type of illness and current treatment:

☐ Respiratory/cardiac _____

☐ Liver/kidney _____

☐ Other, please specify: _____

11. In the opinion of the veterinary surgeon, PRE-operatively what anaesthetic risk group would you classify the patient as?

☐ Class 1 – fit and healthy, no systemic disease.

☐ Class 2 – mild to moderate systemic disease only, eg skin tumour, chronic arthritis, fracture without shock.

☐ Class 3 – severe systemic disease, showing symptoms or limiting activity but not incapacitating, eg moderate hypovolaemia, anaemia or pyrexia, mild to moderate heart failure.

☐ Class 4 – severe systemic disease that is a constant threat to life, eg severe uraemia, toxaemia, hypovolaemia, heart failure.

☐ Class 5 – moribund patient that is not expected to survive 24 hours with or without the operation, eg extreme sepsis/shock.

In the light of any information gained from undertaking the procedure, POST operatively would you give the patient the same anaesthetic risk class?

☐ YES ☐ NO, revised risk: ☐

12. Was a pre-operative clinical examination performed? ☐ YES ☐ NO

If YES, by whom was it performed? ☐ VET ☐ NURSE ☐ Other person, please specify: ☐

Please briefly describe any significant clinical findings:

☐

13. Were haematological or biochemical blood tests performed pre-operatively? ☐ YES ☐ NO

If YES, please specify any significant findings and enclose a copy of the results if available:

☐

14. Were thoracic or abdominal radiographs taken perioperatively? ☐ YES ☐ NO

If YES, please specify the radiographs taken and any significant findings:

☐

15. Were any other tests performed preoperatively (eg ECG, ultrasound, urine analysis)? ☐ YES ☐ NO

If YES, please specify the tests performed and any significant results

☐

16. Was the patient starved prior to the procedure? ☐ YES ☐ NO ☐ Not known If YES, for how long? ☐ (hours)

17. Was water withheld prior to the procedure? ☐ YES ☐ NO ☐ Not known If YES, for how long? ☐ (hours)

Section C: Procedure details

In this section we would like to ask a few questions related to the procedure undertaken.

18. Date of admission / / Time of admission (24 hour clock) :

19. Date of procedure / / Date of form completion / /

20. Please classify the procedure type
- ☐ Emergency – requiring immediate surgery on admission.
- ☐ Urgent – operation required within the next 24 hours.
- ☐ Scheduled / Elective - a procedure not requiring attention within the next 24 hours.

21. What procedure was intended?

Was this the procedure performed? ☐ YES ☐ NO If YES, please go to **Q22**

If NO, please briefly describe why the intended procedure was not carried out and what procedure was performed instead (if any).

22. In the opinion of the surgeon, what was the anticipated risk of death from the procedure?

☐ Minimal risk ☐ Low risk ☐ Moderate risk ☐ High risk

23. In the opinion of the surgeon, how difficult was the procedure that was performed?

☐ Simple ☐ Moderate ☐ Difficult ☐ Very difficult

24. Where did the procedure take place?

☐ Theatre ☐ Prep room ☐ Consulting room ☐ Other:

25. Was the procedure performed at the main practice or at a branch?

☐ Main practice ☐ Branch practice – please give branch initials

26. What was the patient's main body position during the procedure

☐ Dorsal recumbency ☐ Left lateral recumbency ☐ Right lateral recumbency ☐ Sternal recumbency

☐ Multiple positions – please describe briefly:

Section D: Anaesthetic drugs and sedatives administered

Now we are going to ask some questions about the drugs given to the patient.

27. For the procedure undertaken did the patient receive sedation only or general anaesthesia?

☐ GENERAL ANAESTHESIA – please now go to **Q28** (defined as complete unconsciousness, allowing ET intubation if required)

☐ SEDATION – please now go to **Q29** (defined as chemical restraint without unconsciousness, ET intubation would not be possible)

28. Was any PRE-MEDICATION given prior to anaesthesia? ☐ YES ☐ NO If NO, please go to **Q29.**

If YES, what drugs were given?

Drug name	Dose	Concentration	Route given	Time given

What was the effect of pre-medication?

☐ No effect

☐ Light sedation – patient calm but still alert

☐ Moderate sedation – patient quiet, able to walk, some ataxia

☐ Heavy sedation – patient recumbent, difficult to rouse

☐ Unconscious

29. Were any INJECTABLE drugs given for INDUCTION or MAINTENANCE of anaesthesia or sedation (other than premedication recorded in Q28)?

☐ YES ☐ NO If NO, please go to **Q30**

If YES, what drugs were given?

Drug name	Dose	Concentration	Route given	Time given

What was the overall effect of these drugs?

☐ No effect

☐ Light sedation – patient calm but still alert

☐ Moderate sedation – patient quiet, able to walk, some ataxia

☐ Heavy sedation – patient recumbent, difficult to rouse

☐ Unconscious

What was the quality of induction of sedation/anaesthesia?

☐ Good - smooth ☐ Moderate ☐ Poor – excitable, some struggling

30. Was an INHALATIONAL anaesthetic used? ☐ YES ☐ NO If NO, please go to **Q31**

If YES, what was used? ☐ Halothane ☐ Isoflurane ☐ Other, please specify: ☐

When was the inhalation agent given? ☐ Induction only ☐ Maintenance only ☐ Both induction and maintenance

31. Was the patient's airway intubated? ☐ YES ☐ NO If NO, please go to **Q32**

If YES, was it a cuffed or uncuffed tube? ☐ Cuffed ☐ Uncuffed

Was local anaesthetic used to desensitise the larynx? ☐ YES ☐ NO ☐ Not known

32. Was oxygen supplied during the procedure? ☐ YES ☐ NO

33. Was nitrous oxide supplied during the procedure? ☐ YES ☐ NO

34. Was an anaesthetic circuit used during the procedure? ☐ YES ☐ NO

If YES, what circuit was used (please specify)? _____

35. What type of ventilation was mainly used? ☐ Spontaneous breathing ☐ Positive pressure ventilation

36. Were any ANALGESICS or OTHER DRUGS administered PERI-operatively? ☐ YES ☐ NO If NO, please go to **Q37**
(excluding those given and recorded during pre-medication, Q28)

If YES, what analgesics or other drugs were given?

Drug name	Dose	Concentration	Route given	Time given

37. Was an intravenous catheter placed PERI-operatively? ☐ YES ☐ NO

38. Were fluids administered PERI-operatively? ☐ YES ☐ NO If NO, please go to **Q39**

If YES, please state the type of fluids: _____ the amount given: _____ ml

When were they given? (please tick all appropriate) ☐ Pre-operatively ☐ During the procedure ☐ Post operatively

By which route? ☐ Intravenous ☐ Subcutaneous ☐ Other: _____

39. Was a full anaesthetic machine check performed before the procedure? ☐ YES ☐ NO ☐ Not applicable

Section E: Monitoring of anaesthesia and sedation

In this section we would like to ask a few questions about the monitoring of the patient during the procedure.

40. Was the patient monitored during the procedure? ☐ YES ☐ NO If NO, please go to **Q43.**

If YES, who monitored the patient?

☐ Operating Vet ☐ Separate Vet ☐ Nurse ☐ Other: _____

What other duties was this person doing at the time?

☐ No other duties ☐ Performing the procedure ☐ Assisting with the procedure ☐ Answering the telephone

☐ Other, please specify: _____

41. Is there a written record of the anaesthetic? ☐ YES ☐ NO If YES, please attach a copy of the anaesthetic record.

42. What methods of monitoring were used during the procedure?

☐ Finger on pulse
☐ Pulse oximeter
☐ Observation of breathing / reservoir bag
☐ Electrocardiogram
☐ Oesophageal / standard stethoscope
☐ Arterial blood pressure – direct method
☐ Respiratory rate monitor
☐ Arterial blood pressure – indirect method (eg Doppler, DINAMAP)
☐ Other, please specify: _____

Section F: Recovery from anaesthesia and sedation

In this section we would like to look at aspects of the patients recovery after the procedure.

43. Time of termination of the procedure: (24 hour clock): :

44. Duration of anaesthesia or sedation (in minutes):

45. Was a reversal agent given at the end of the procedure? ☐ YES ☐ NO

If YES, what drug was given? Dose:

46. Please give the approximate time from termination of the procedure until the patient reached the following:

Sternal recumbency: min Standing: min

47. What was the quality of recovery? ☐ Poor – very violent, fitting etc ☐ Moderate - minimal excitement ☐ Good – smooth

48. Where was the patient placed to recover?

☐ Kennel/cage ☐ Theatre ☐ Prep room ☐ Other, please specify:

49. Was the patient observed during recovery? ☐ YES ☐ NO If NO, please go to **Q50**

If YES, Who observed the recovery? ☐ Vet ☐ Nurse ☐ Other, please specify:

How often was the patient checked whilst recovering?

☐ Continuously ☐ Every 5 minutes ☐ Every 10 minutes ☐ Other, please specify:

50. Was the patient's temperature taken on recovery? ☐ YES ☐ NO If YES what was it? ^{0}C

51. Were there any NONFATAL serious perioperative complications (eg collapse, hypotension, respiratory obstruction or depression, pulmonary aspiration, fitting, or any problems with ET intubation)?

☐ YES ☐ NO If NO, please go to **Q52.**

If YES, when did this occur? ☐ After premedication ☐ During the procedure ☐ On recovery

What type of complication(s) occurred and what were the treatment and outcome (please specify)?

☐ CNS (eg fitting): _____

☐ Cardiopulmonary: _____

☐ Other, please specify: _____

_____

Section G: Personnel details

Here we are interested in the details of the people involved in the procedure.

52. Please give the initials of the person completing the questionnaire:

Is this the: ☐ Veterinary surgeon ☐ Anaesthetist ☐ Other, please specify:

53. Please give the initials of the MAIN VETERINARY SURGEON involved in the procedure:

How many procedures did they perform on the day?

If on call, were they called out overnight? ☐ YES ☐ NO ☐ Not on Call

How familiar were they with the anaesthetic/sedation used? ☐ Very familiar ☐ Familiar ☐ Unfamiliar

Please state their qualifications: Year of qualifying:

Are they a principal / partner, assistant, locum or other?

☐ Principal / Partner ☐ Assistant ☐ Locum ☐ Other, please specify:

54. Please give the initials of the ANAESTHETIST (person responsible for monitoring the patient):

Is this the same person who undertook the procedure (Q53)? ☐ YES ☐ NO If YES, please go to **Q55.**

If NO, how many procedures were they involved with on the day?

If on call, were they called out overnight? ☐ YES ☐ NO ☐ Not on Call

How familiar were they with the anaesthetic/sedation used? ☐ Very familiar ☐ Familiar ☐ Unfamiliar

Please state their qualifications: Year of qualifying:

Are they a vet or a veterinary nurse? ☐ VET ☐ NURSE ☐ Other, please specify:

If a veterinary nurse, are they? ☐ Qualified ☐ Trainee ☐ Unqualified

55. Were there any OTHER persons involved in the procedure? ☐ YES ☐ NO If NO, please go to **Q56 (fatalities only)**

If YES, please state their initials:

Were they a vet or a nurse? ☐ VET ☐ NURSE ☐ Other, please specify:

What were they doing? Please specify:

If this is a CONTROL form, thank you for taking the time to complete it. Please now send it back to Dave Brodbelt, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk, CB8 7UU in a prepaid envelope supplied. If this is FATALITY please complete the last page.

Section H: Fatality details **Please complete this section for a DEATH / PTS ONLY**

56. Did the patient die or was it euthanased? ☐ Died ☐ Euthanased
In the opinion of the veterinary surgeon, was this due:

☐ Solely as a result of anaesthesia or sedation?

☐ Primarily as a result of anaesthesia or sedation?

☐ Only partly as a result of anaesthesia or sedation?

57. When did the patient die? Time: : (24 hour clock) Date: / /

Was this: ☐ After premed ☐ During sedation/anaesthesia ☐ On recovery
If the patient died please go to **Q58**

If the patient was EUTHANASED, why was it euthanased?
If EUTHANASED, please now go to **Q64**

58. Where did the patient die?

☐ Theatre ☐ Prep room ☐ Kennel ☐ Home ☐ Other:

59. Did the patient show any abnormal clinical signs, just prior to death? ☐ YES ☐ NO

If YES, please specify:

60. Was there an ECG on the patient at the time of death? ☐ YES ☐ NO

If YES, what was the ECG diagnosis?

61. Was any procedure being performed around the time of death? ☐ YES ☐ NO

If YES, please specify:

62. If applicable, what was the vaporiser setting just before the complication? %

63. What was the cause of death? (please specify)

☐ Cardiac complications:

☐ Respiratory complications:

☐ Renal / liver complications:

☐ Other:

☐ Unknown

64. Was a post mortem examination performed? ☐ YES ☐ NO Please enclose a copy of the report if available

If YES, what were the findings?

65. Please add any further comments in the space below that you think would be helpful.

Thank you very much for completing this questionnaire.

Please return the completed questionnaire to Dave Brodbelt, CEPSAF, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU in the prepaid envelope supplied.

Appendix 2.4 Case Definition and Criteria for Independent Review Panel

1. Case Definition

ALL perioperative DEATHS (including patients euthanased) within 48 hours of termination of the procedure EXCEPT for: Patients that DIED or were EUTHANASED for inoperable surgical or pre-existing medical conditions, where anaesthesia or sedation did not contribute to the death or decision to euthanase. If anaesthesia / sedation can NOT be reasonably excluded as a contributory factor then the death / euthanasia should be considered an anaesthetic related death.

2. Evidence for an association with anaesthesia / sedation

a. Specific evidence of contribution of anaesthesia to death: Evidence from the description of the fatality. Post-mortem evidence.

b. Timing of death

During anaesthesia - less evidence required to classify as a case.

Postoperative – greater proximity to end of anaesthesia suggests greater support for classifying as a case.

c. Procedure contribution – Less evidence of procedural contribution to death suggests less evidence required to classify as a case.

d. Patient Status

Health status – healthier patients require less evidence to classify as a case.

Emergency status – lower urgency requires less evidence to classify as a case.

e. Cause unknown – include as case if there are no known cause of death.

3. Examples

a. Cases

Intraoperative deaths: Respiratory obstruction and death. Cardiac arrest with no evidence of procedural cause.

Postoperative deaths: No evidence of cause of death. Renal or liver failure occurring when minimal pathology was present. Neurological complications or fitting requiring euthanasia – where no evidence of neurological pathology was present preoperatively.

b. Non Cases

Intraoperative deaths: Uncontrolled haemorrhage during splenic tumour removal. Euthanasia for inoperable surgery or owner declined treatment

Postoperative deaths: Gastric-dilatation-volvulus recovering to preoperative state that dies 18 hours later of toxic complication. Peritonitis diagnosed and death at 12 hours postoperatively.

Appendix 2.5 Causes of Death Classification

Classification of PRIMARY initiating cause of death with respect to physiological system and the likely specific cause:

a. Cardiovascular Complication: Cardiac arrest / Circulatory failure.

b. Respiratory Complication: failure of delivery of O_2 to and removal of CO_2 from alveoli and failure of alveolar gas exchange. Includes: airway obstruction, failure of ventilation, hypoxia, failure of pulmonary gas exchange.

c. Cardiovascular or Respiratory Failure – insufficient evidence to categorically conclude which of these two causes was the primary and which was secondary cause.

d. Renal Failure

e. Liver Failure

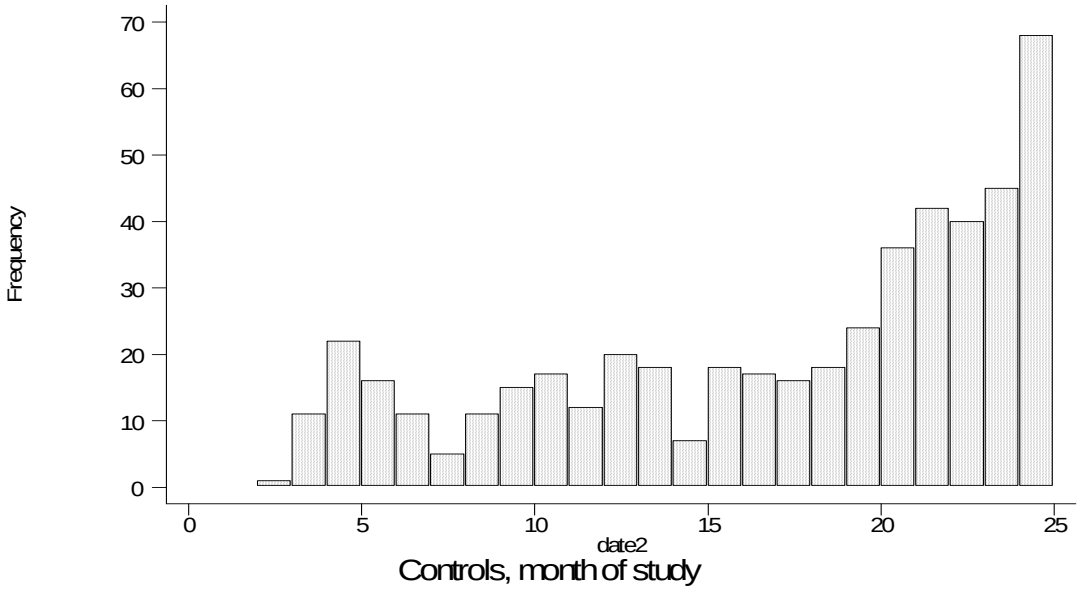
f. Neurological Complication: Uncontrolled fitting requiring euthanasia, failure to regain consciousness requiring euthanasia.

g. Unknown

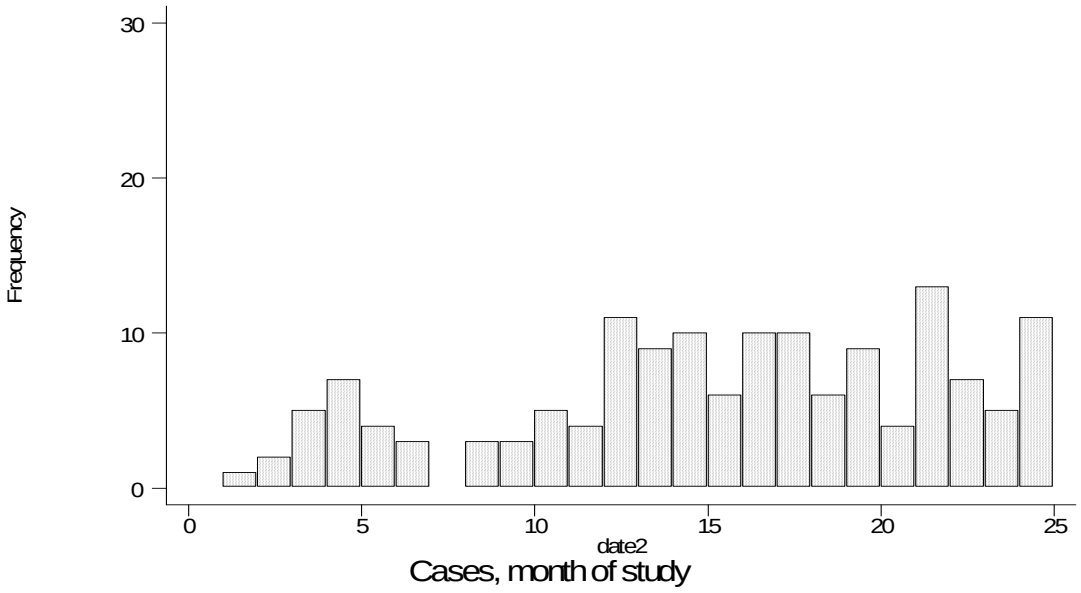
Appendix 2.6 Distribution of Cases and Controls over the Study Period

1. Number of Controls and Cases randomly selected monthly in Dogs

a. Controls

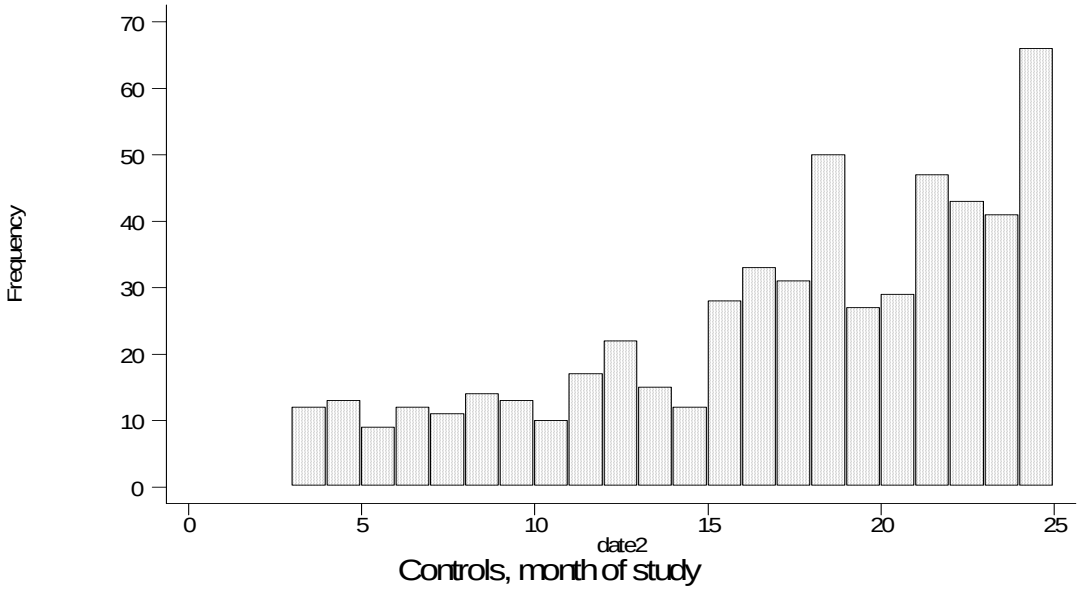


b. Cases

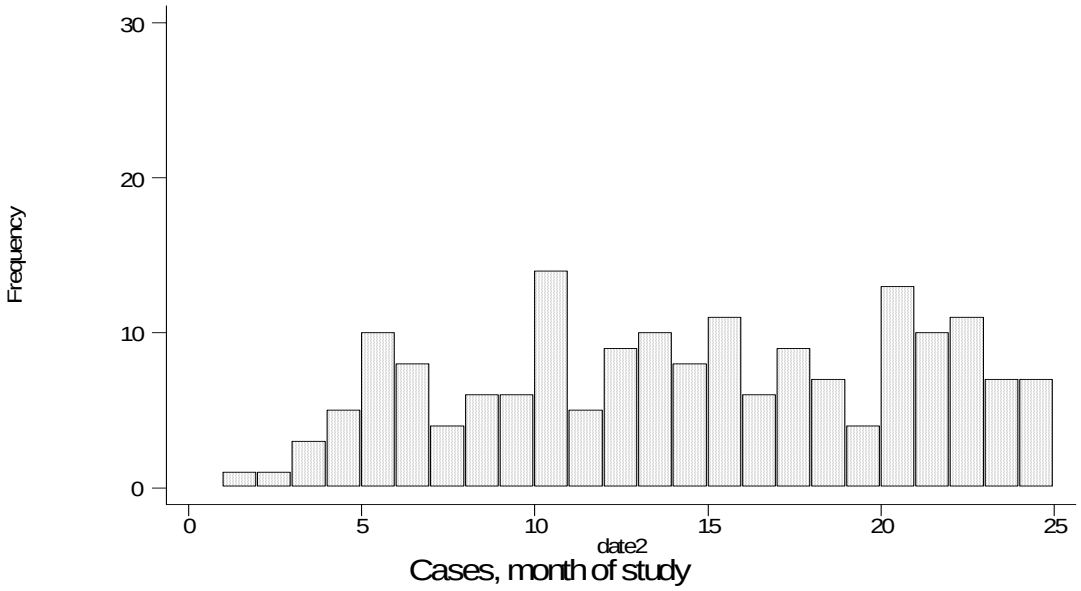


2. Number of Controls and Cases randomly selected monthly in Cats

a. Controls

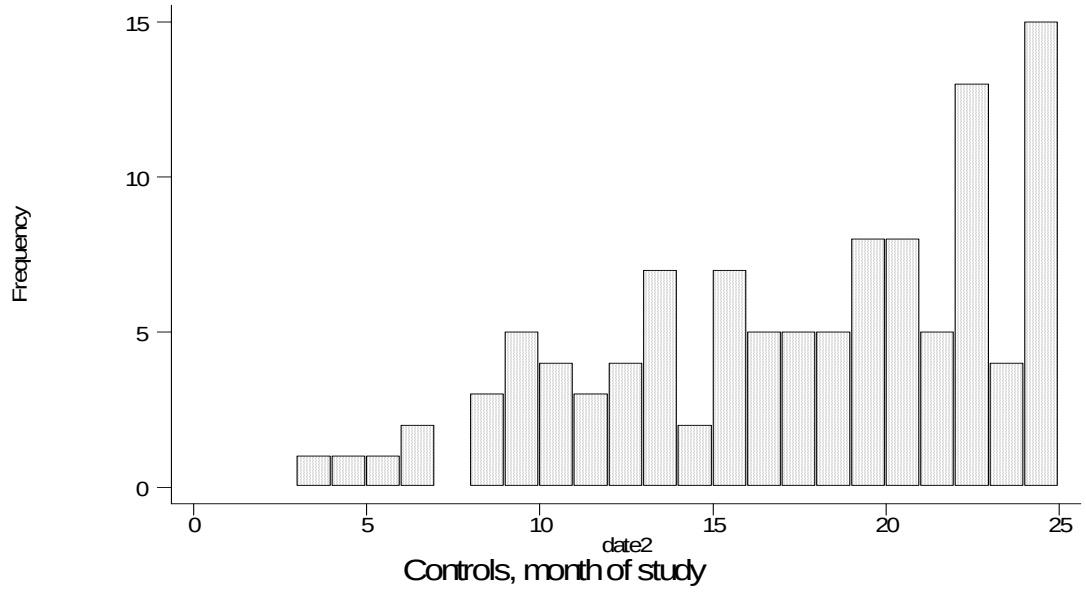


b. Cases

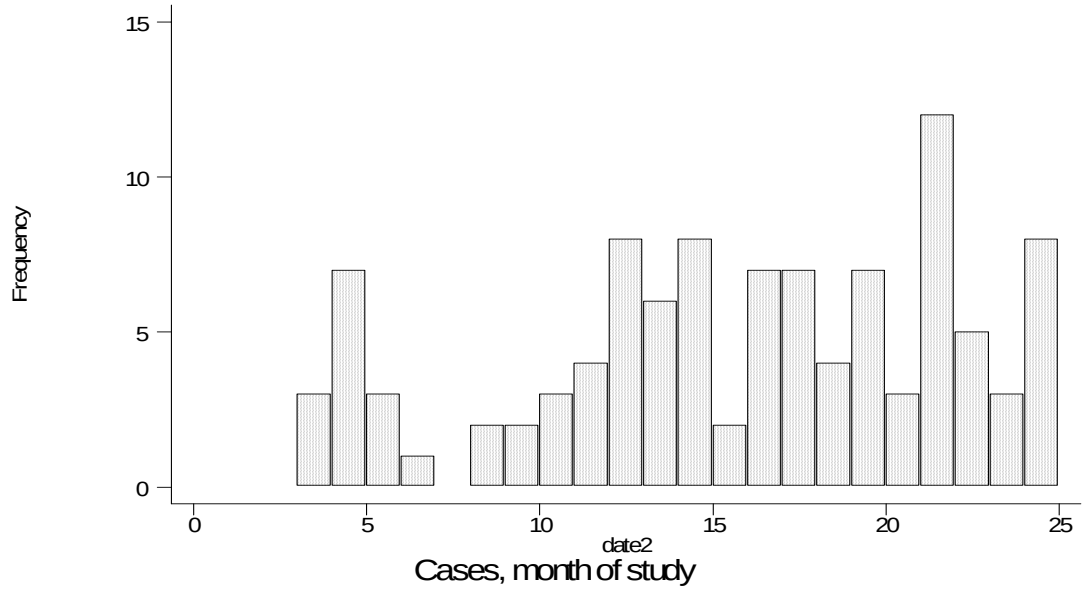


3. Number of Controls and Cases randomly selected monthly in Sick Dogs

a. Controls

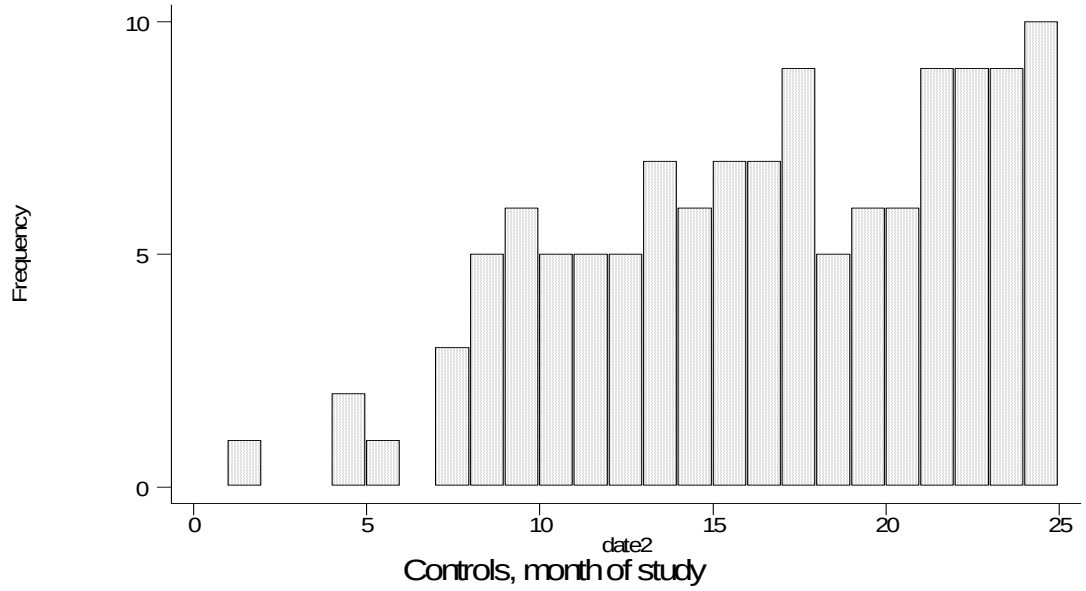


b. Cases

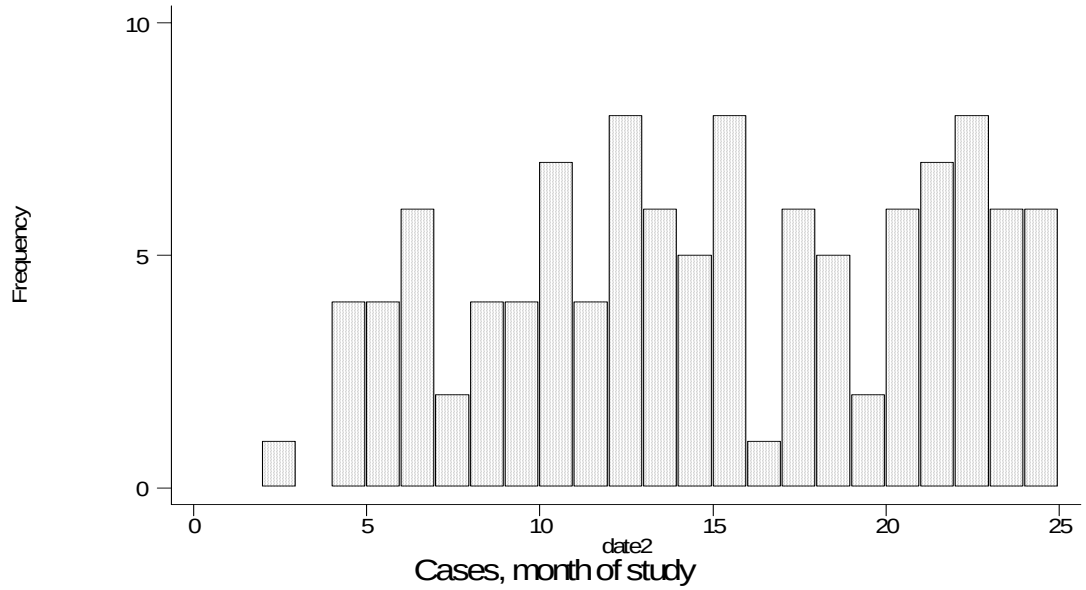


4. Number of Controls and Cases randomly selected monthly in Sick Cats

a. Controls



b. Cases



Appendix 2.7 CEPSAF Practice Survey Questionnaire

CEPSAF

Confidential Enquiry into Perioperative Small Animal Fatalities

Practice Survey Form

Clinic number: ☐

Date: ☐

A. Clinic Characteristics:

1. Type of practice? ☐ Small animal practice ☐ Mixed practice: % Small Animal= _____

   ☐ RCVS Hospital ☐ BSAVA standard ☐ Neither

   % First opinion: _____ % Referral: _____

2. Does the practise use computerised case records? ☐ YES ☐ NO
   If YES, What computer system is used? _____

3. How many full time vets (or equivalence) are there at the practice doing small animal work? _____

   Do any have any further professional qualifications? ☐ YES ☐ NO

   If YES, please state the number of vets and qualifications: _____

   Do any have further qualifications in anaesthesia? ☐ YES ☐ NO

   If YES, please state the number of vets and qualifications: _____

4. How many full time nurses (or equivalence) are there at the practice doing SA work? _____

   How many are qualified? _____ How many are training? _____

5. How many anaesthetics and sedations do you routinely do each week (total for the practice)?

Dogs:	General Anaesthetics:	☐	Sedations:	☐
Cats:	General Anaesthetics:	☐	Sedations:	☐
Exotics:	General Anaesthetics:	☐	Sedations:	☐

6. Are there any branch surgeries? ☐ YES ☐ NO
   If NO, please go to **Q7**.
   If YES, How many branches are there? _____

   Are animals sedated or anaesthetised at the branch surgeries? ☐ YES ☐ NO
   If YES, at how many branches are anaesthetics or sedations undertaken? _____

7. What percentage of your out of hours cover do you do yourselves? _____
   If you do not do all your own emergency cover what type of centre does the rest? _____
   Is there a vet / nurse / other on the premises 24 hours a day? _____

B. Anaesthetic Practices:

8. What drugs do you routinely use for sedation?
   a. Dogs _____
   b. Cats _____

9. What drugs do you routinely use for premedication prior to general anaesthesia?
   a. Dogs _____
   b. Cats _____

10. What drugs do you routinely use for induction of anaesthesia? (please include percent of total drugs used)?
   a. Dogs _____
   b. Cats _____

11. What drugs do you routinely use for maintenance of anaesthesia (please include percent of use)?
   a. Dogs _____
   b. Cats _____

12. What is you routine rabbit anaesthetic protocol: _____
   (including premed, induction, intubation method, gas used)

13. Do you routinely intubate your patients? Dogs ☐ YES ☐ NO
   Cats ☐ YES ☐ NO
   If YES, Do you use cuffed or uncuffed tubes? Dogs ☐ Cuffed ☐ Uncuffed
   Cats ☐ Cuffed ☐ Uncuffed

14. Do you routinely use oxygen? Dogs ☐ YES ☐ NO
   Cats ☐ YES ☐ NO

15. Do you routinely use nitrous oxide? Dogs ☐ YES ☐ NO
   Cats ☐ YES ☐ NO

16. Which circuits do you regularly use? (please tick all appropriate)

   ☐ Circle ☐ To and Fro

   ☐ T piece ☐ Bain

   ☐ Magill ☐ Lack ☐ Other: _____

17. How many anaesthetic machines does the main practice have? _____
   How many have a low-oxygen warning device (whistle)? _____

   How many BRANCHES have an anaesthetic machine? _____ No. of machines: _____
   How many have a low-oxygen warning device? _____

18. Does the practice have a ventilator? ☐ YES ☐ NO
   If YES do you use it regularly? ☐ YES ☐ NO

C. Patient Management and Monitoring

19. Do you routinely place an intravenous catheter? Dogs ☐ YES ☐ NO
Cats ☐ YES ☐ NO

20. Would you ever give fluids to your patients? ☐ YES ☐ NO
If YES, to which patients? _____

21. What percentage of you patients have preoperative blood tests? _____ Dogs _____Cats
Are these patients generally?

☐ Higher risk ☐ Older patients ☐ Any patient ☐ Other: _____

Which tests do you routinely do? _____

22. Do you weigh the majority of your patients? DOGS? ☐ YES ☐ NO
CAT? ☐ YES ☐ NO

23. Who sedates / premeds patients? ☐ Vet ☐ Nurse ☐ Both ☐ Other: _____

24. Who induces anaesthesia? ☐ Vet ☐ Nurse ☐ Both ☐ Other: _____

25. Who routinely monitors the anaesthetics and sedations?

☐ Vet ☐ Nurse ☐ Both ☐ No one ☐ Other: _____

26. Do patients have anaesthetic records? ☐ always ☐ sometimes ☐ never

27. What anaesthetic monitoring equipment do you have? Which of these do you use regularly?

	Have	Use Regularly
Oesophageal / standard stethoscope	☐	☐
Respiratory rate monitor	☐	☐
Pulse Oximeter	☐	☐
Electrocardiogram	☐	☐
Arterial Blood Pressure – Type: _____	☐	☐
Other: _____	☐	☐

28. Does the practice have an emergency box? ☐ YES ☐ NO
If YES, Where is it kept? _____
How often is it checked?

☐ Once a week ☐ Once a month ☐ Every six months ☐ Other: _____

Is there a protocol sheet for CPR in the theatre? ☐ YES ☐ NO
Do you have facilities for suction? ☐ YES ☐ NO

29. Have you had any anaesthetic / sedation-related deaths in the last year? ☐ YES ☐ NO
If YES, how many? _____ Dogs _____ Cats
_____ Other species

Thank you for completing this questionnaire, please now post it back in one of the postage paid envelopes to Dave Brodbelt, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU, Fax 01638 555 659.

Appendix 6.1 Drug dose associations with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Acepromazine dose	0 – 0.02 mg/kg	15	33	1		
	0.02 - 0.03 mg/kg	22	93	0.52	0.24 – 1.13	0.09
	0.03 – 0.05 mg/kg	23	146	0.35	0.16 – 0.75	0.01
	0.05 - Max	10	110	0.20	0.08 – 0.51	<0.001
	Trend			0.59	0.45 – 0.78	<0.001
	Trend adj ASA2			0.83	0.61 – 1.14	0.25
	LRT P value					0.01
Medetomidine Dose	0 – 0.01 mg/kg	4	17	1		
	0.01 mg/kg - max	4	43	0.40	0.09 – 1.81	0.22**
Propofol dose	0 - 3 mg/kg	42	37	1		
	3 - 4 mg /kg	20	58	0.30	0.15 – 0.61	<0.001
	4 - Max	41	195	0.19	0.10 – 0.34	<0.001
	Trend			0.54	0.45 – 0.66	<0.001
	Trend adj ASA2			0.73	0.56 – 0.94	0.02
	LRT P value					<0.001
Thiopentone dose	0 – 7.5 mg/kg	5	10	1		
	7.5 – 10 mg/kg	4	19	0.42	0.09 – 2.02	0.26
	10 – max	5	78	0.13	0.03 – 0.60	0.01
	Trend			0.28	0.13 – 0.61	<0.001
	Trend adj ASA2			0.33	0.15 – 0.75	<0.001
	LRT P value					<0.001

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables. **Fisher's exact test and exact 95% confidence interval.

Appendix 6.2 The association of drugs with anaesthetic-related death in Dogs

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Acepromazine	No acepromazine	78	95	1		
	acepromazine	70	392	0.2	0.1 – 0.3	<0.001
	Adjusted for ASA2			0.5	0.3 – 0.8	0.01
Medetomidine	No medetomidine	140	427	1		
	Medetomidine	8	60	0.4	0.2 – 0.9	0.02
	Adjusted for ASA2			0.4	0.2 – 1.1	0.08
Benzodiazepine	No benzodiazepine	132	464	1		
	diazepam	10	15	2.4	1.0 – 5.4	0.04
	midazolam	6	8	2.6	0.9 – 7.8	0.07
	LRT P value					0.04
Opioid						0.06
	No opioid	26	61	1		
	partial agonist	77	306	0.6	0.4 – 1.0	0.05
	pure mu agonist	45	120	0.9	0.5 – 1.6	0.66
NSAIDs						<0.001
	No NSAID	92	154	1		
	Carprofen	36	222	0.3	0.2 – 0.4	<0.001
	Meloxicam	20	111	0.3	0.2 – 0.5	<0.001
Thiopentone	No thiopentone	134	367	1		
	thiopentone	14	120	0.3	0.2 - 0.6	<0.001
	Adjusted ASA2			0.7	0.4 – 1.4	0.34
Propofol	No propofol	35	168	1		
	propofol	113	319	1.7	1.1 – 2.6	0.01
	Adjusted ASA2			1.1	0.6 – 1.8	0.86
Rectal Temperature (C)		37.08 (1.07)	38.34 (8.12)			0.57
Vet Year of Qualification						0.60
	1966 – 1984	33	94	1		
	1985 – 1994	49	149	0.94	0.56 – 1.56	0.80
	1995 – 1999	43	158	0.78	0.50 – 1.31	0.34
	2000 - 2003	20	81	0.70	0.37 – 1.32	0.27
	Unknown	3	5			
Anaesthetist Year of Qualification						0.77
	1966 – 1984	10	25	1		
	1985 – 1994	16	55	0.73	0.29 – 1.84	0.50
	1995 – 1999	32	82	0.98	0.42 – 2.27	0.95
	2000 - 2003	49	121	1.01	0.45 – 2.27	0.98
	Unknown	41	204			

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables.

Appendix 7.1 The association of drug dose with anaesthetic-related death in cats

Variable	Categories	Cases	Controls	OR*	95% CI*	P value
Acepromazine dose						0.12
	0.001 – 0.2 mg/kg	3	15	1		
	0.02 – 0.03	16	33	2.4	0.6 – 9.9	0.20
	0.03 - max	70	288	1.2	0.3 – 4.3	0.76
Medetomidine dose						0.35
	0.001 – 0.03 mg/kg	5	13	1		
	0.03 – 0.06	11	72	0.4	0.1 – 1.4	0.39
	0.06 - max	12	63	0.5	0.1 – 1.7	0.50
Thiopentone dose						0.01
	0 – 7.5 mg/kg	4	1	1		
	7.5 - 10	4	6	0.2	0.0 – 2.8	0.16
	10 - max	10	46	0.1	0.0 – 0.7	0.002
Propofol dose						<0.001
	0 – 5 mg/kg	43	53	1		
	5 – 7 mg	31	117	0.3	0.2 – 0.6	<0.001
	7 - max	26	86	0.4	0.2 – 0.7	0.001
Saffan dose						0.04
	0 – 4 mg/kg	3	9	1		
	4 – 8 mg	2	33	0.2	0.0 – 1.4	0.06
	8 - max	4	8	1.5	0.2 – 9.3	0.66
Ketamine dose						0.26
	0 – 3 mg/kg	7	16	1		
	3 – 6 mg	12	64	0.4	0.1 – 1.3	0.12
	6 - max	5	30	0.4	0.1 – 1.4	0.14

*Odds ratios (OR) and 95% confidence intervals (CI) are reported. Likelihood Ratio Test (LRT) P values are reported for multiple category variables at the top of 'P Value' column.

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