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Meta-analysis — a systematic and quantitative review of animal experiments to maximise the information derived

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Abstract

Meta-analysis provides a tool to statistically aggregate data from existing randomised controlled animal experiments. The results can then be summarised across a range of conditions and an increased pool of experimental data can be subjected to statistical analysis. New information can be derived, but most frequently the results are a refinement of existing knowledge. By designing experiments and reporting protocols, so that they have the capability of being useful to meta-analyses, maximum benefit can be derived from individual randomised controlled experiments, which may individually have little statistical power, and new avenues for productive research identified. The methodology for meta-analysis is derived from clinical trials in the medical sciences. Now that there is substantial output from animal science experiments, there is an opportunity to apply the technique to these and reduce the need for further experimentation. This paper describes the contribution of meta-analysis to the reduction of animals in research and provides details on data collection, analysis, the models used, and on interpreting and reporting the results. Three applications of meta-analysis to the field of animal science are also briefly described. First, the impact of undernutrition on the production and composition of milk from dairy cows confirmed existing knowledge about partitioning scarce nutrients to milk yield and live weight. Second, increased absorption of cadmium — a widespread toxic element — from organic sources was detected in sheep, which was previously untested. Third, no significant relationships were found between common indicators of undernutrition and weight, and condition score in cattle suggesting that the common indicators used are not suitable as evidence of long term undernutrition. This paper concludes that opportunities exist to increase the information gained from animal experiments by subjecting the results to meta-analysis, particularly if this can be anticipated in advance of study protocols being constructed.

Keywords: *animal science, animal welfare, experimentation, meta-analysis, research techniques, statistics*

Introduction

Inconsistent experimental findings commonly present difficulties in the interpretation of animal science research, which is often suspected to be due to insufficient statistical power (Jennions & Møller 2003) and sometimes a lack of independence in the subjects — most of which are social animals kept in groups (Phillips 1998, 2002). Despite this, animal science research is growing at a rapid rate. With new experimental tools for genetic modification, improved reproduction and nutrition research techniques, and the expansion of animal science research into many developing countries, the number of animal science experiments is increasing in spite of the concerns of many about the ethical validity of the research. At the same time, with the objectives for animal science research changing from increased productivity of domesticated animals to enhancing the sustainability of production systems, in terms of their ecological and ethical impact and the improvement of human health, animal science researchers are exhorted to embrace an interdisciplinary approach to their particular specialisations (Webster 2002). Remaining informed of the results of large numbers of randomised, controlled experiments from multiple disciplines can be difficult and requires the findings to be published, to inform researchers in the field in question, and for the literature to be regularly reviewed. Journals have arisen specifically for reviews, for example, *Animal Health Research Reviews* and *Nutrition Research Reviews*; however, even critical literature reviews contain an element of subjectivity, which may mislead researchers on important issues. Meta-analysis is a tool to reduce such subjective assessment and replace it with a rigorous statistical analysis of data collated from all the relevant, extant experiments.

In meta-analysis, an experimental average, or a treatment average, is usually the experimental unit, rather than the animal, which is normally the replicate in randomised, controlled experiments. This expands the population base, which may therefore contain animals of different breeds, ages, and sometimes even species. Therefore, the results of meta-analysis are often generic, sometimes with factors identified that enumerate the variation attributable to circumstances of the field of application. Thus the results can be applied in a wide variety of conditions and with greater confidence than results from a limited number of isolated experiments. Coefficients relating cause and effect may be determined for confirmed responses where only qualitative effects were previously known or suspected. Occasionally, researchers use the term 'meta-analysis' to refer to an across species analysis within an ecosystem (Gram *et al* 2001), but this is not the usual meaning of the term, which is "a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method" (Cook *et al* 1995).

Despite the increasingly widespread application of standard scientific procedures and experimental methodology, experiments still differ considerably in the number of animals used, the type of animal and their management. The most difficult task for meta-analysts is to decide which experiments can be safely introduced into the statistical model and which should be rejected. Meta-analysis research in animal science is best conducted by a combination of an experienced biologist and a statistician trained in the relevant techniques; some biologists may not be sufficiently knowledgeable in research methodology to be able to evaluate the merits of a wide variety of experimental methods. However, possibilities exist within meta-analysis to investigate the impact of individual experiments and to decide *post hoc* whether the results of particular experiments should be discarded. Some experiments are inevitably of greater value than others, and it is standard practice to weight experiments using an estimate of the magnitude of the error in individual experiments, where this is known.

When conducting meta-analyses, the limitations of scientific reports from different sources rapidly become apparent. Varying standards in reporting are also assumed by different authors. Much could be done to improve the knowledge gained from individual experiments, and their eventual incorporation into a meta-analysis, if journal editors' could be persuaded to insist on more uniform standards of reporting. As well as missing information, there are potential problems with the incorrect use of statistical tests, failure to examine the structure of the data before analysis, repeated publications of trials containing data that are inconsistent, and authors that are unwilling or unable to correct the deficiencies in their publication when subsequently contacted. The development of standards for research practice by industry, government and other bodies may help to reduce the problems. Furthermore, researchers are often being evaluated on the quantity of their publications and the quality of the journals that they are published in; therefore, standards and the completeness of reporting should increase.

The current transition from paper to electronic media for scientific journals should reduce the space restrictions on individual articles. This would allow a standard format for providing adequate background data on the experimental conditions, as well as treatment responses and their associated error terms to be provided in sufficient detail for incorporation into meta-analyses (see list of reporting requirements in Data collection). The aim should not only be to allow experiments to be evaluated for their immediate results, but also for the possibility of incorporation into a meta-analysis when a sufficient number of similar trials have accumulated.

Materials and methods

Standards for conducting meta-analysis in medical science have recently been enunciated (Cook *et al* 1995; Moher *et al* 1999). Followed carefully, meta-analyses will produce valuable summaries of overall effects in defined populations. Meta-analyses have also been used to identify best practice in research, for example, proving the necessity of double-blind procedures in clinical research (Benignus 1993). Recently, meta-analysis has begun to be applied to the animal sciences, even extending to behaviour research (eg Shuker *et al* 2004). In this paper, the main requirements for conducting an effective meta-analysis are outlined and three attempts to apply meta-analysis to animal science are described, together with the difficulties that may be encountered by the meta-analysts.

Data collection

The first step in initiating meta-analysis, as with any research, is to pose the question clearly and simply. The desirable population, treatments and outcomes should also be specified. Second, the search strategy should be confirmed, which is likely to rely on electronic databases of published research, but can also include unpublished research, review articles, conference proceedings, dissertations, books, expert informants, patent listings and journal indices. Incorporation of literature from varied sources can reduce publication bias, which occurs because trials that have generated significant results are more likely to be published than those that do not, thereby artificially inflating the magnitude of the effect (Moher *et al* 1999).

Recent modelling techniques allow the heterogeneity of the results to be tested statistically, facilitating an assessment of publication bias (Munafo *et al* 2004). Examination of a 'funnel plot' of sample size against response should demonstrate a reduction in the diameter of the funnel with sample size and a corresponding increase in the accuracy of determining the response. This should allow a visual assessment of variation in responses, but there are often insufficient studies with large numbers that should form the apex of the funnel. However, there may be true heterogeneity and other factors, such as multiple publications or poor design of small studies, which create bias. Alternatively, the distribution of responses can be compared with the Normal Distribution and statistical tests performed to determine the number of zero effect publications that would alter the conclusions (Sutton *et al* 2000).

The distribution of results can be manipulated, so that small studies fit the trend of larger studies, but questionable assumptions are necessary. It is best to avoid publication bias altogether by ensuring that all relevant studies, published and unpublished and in any language, are found. However, studies may be rejected for publication for reasons other than a lack of significant results, and inclusion of studies of low reliability may artificially bias the results toward a zero effect. The referees of papers submitted to journals should also be made more aware of

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the potential bias that can be caused by rejecting papers simply because they do not contain statistically significant differences between treatments.

Language constraints must also be considered in relation to possible publication bias within the limitations of the project budget. Publications in English show more of a bias toward statistically positive results than publications in other languages, thereby possibly overestimating treatment effects (Moher *et al* 1999). Phrases and keywords entered into electronic search databases must be chosen with great care, taking into account different spellings of keywords (eg 'behaviour' and 'behavior'), local terms for production animals (eg hog, swine, pig etc), common and Latin names, singular and plural etc. Most meta-analyses use a sequential screening process, initially identifying articles with certain keywords and reducing the selection process by reading abstracts and then entire articles to identify those with the relevant information. Usually an inclusive approach is adopted at this stage, because individual experiments can be more readily rejected at a later stage than omitted experiments can be reintroduced into the dataset if the criteria for inclusion changes because of unforeseen circumstances.

Abstracts are usually stored on a literature database package, such as Endnote, which can discard duplicates when the results of searches on different electronic databases are introduced. Quality assessment is an important part of the reading of articles, and may be indicated by the detail and repeatability of the trial methodology, journal quality and the quality of other publications by the author. Some authors publish their results in several different articles, even with discrepancies between articles, and the meta-analyst has to determine the most reliable source of information; authors should be contacted for further details if necessary. An electronic spreadsheet package, such as Excel, linked to the database is usually used to store extracted data, which should include the author(s), date and place of the articles (ie journal name for published articles or location for unpublished articles), date that it was read, duration of the experiment, the species, age, gender, number of experimental animals, their physiological state, any health problems that the animals suffered, treatment applications, variance, and response variables (eg live weight gain, milk yield etc). Standard formulae are used to convert experimental units to a common form, although measurements of different physical characteristics can cause difficulties, for example, lux and photons in light measurement.

Data analysis

Analytical methods for animal science meta-analyses have developed rapidly from simple linear models (eg Phillips 1991) to hierarchical regression models that incorporate information on variance (Prankel *et al* 2004). Analysis is usually in the form of a random effects model, which assumes that there is random variation in the response to a treatment, and attempts to determine the factors responsible for the variation. Fixed effects models, where the treatment effect is assumed to be the same in each study, are not applicable to the wide range of conditions usually included in a random effects model. Any variation in responses in fixed effects models is assumed to arise from sampling, analytical or other design problems. Determining whether fixed or random effects models are more appropriate may be performed using the χ^2 test for heterogeneity, even though it has limited statistical power. Mixed linear models of fixed covariates, which explain some of the heterogeneity, together with a random component to accommodate unexplained heterogeneity, may offer the best solution (Abrams & Sanso 1998). Bayesian analyses, in which background or prior information is included, are often favoured, particularly in cumulative meta-analyses. Cumulative analysis will indicate the most relevant studies, and determine how many more studies showing similar results would be required to achieve significance. A power calculation can be performed to indicate the number of studies required to detect significant differences of varying magnitude, as well as the chance of type 1 statistical errors (Smith *et al* 1995).

Some researchers argue that Bayesian analysis takes into account all the uncertainty regarding model parameters; therefore, a random effects model is most appropriate if Bayesian analysis is performed (Abrams & Sanso 1998). If necessary, fixed effects models can be compared with random effects models to determine which is most appropriate.

Weighting the model

In a random effects model, the experimental units are often weighted according to the reciprocal of the sum of the between and within study variance, which improves the statistical power (Sanchez-Meca & Marin-Martinez 1998) but which may over-represent studies with extreme risk in binary outcome models (Tang 2000). In a fixed effects model, the between study variance is assumed to be zero. Simple weighting on the basis of sample size is possible (eg Moodie *et al* 2004), but may underestimate treatment effects when there are outlier sample sizes (Osburn & Callender 1992). Variance measures are often not included in lesser quality publications, or variance may not be a relevant statistic because the data is not normally distributed. Variance can be estimated from a model of the relationship between variance and n, the number of replicates, which is one of the most influential components. However, if too few experiments contain variance or sample size estimates, as was the case in the meta-analysis of Tudoreanu and Phillips (2004), no weighting is possible, but a simple meta-regression can still be carried out. If too few experiments report reliable averages, as well as limited data on variances and sample sizes, a qualitative report of the relevant literature may be all that is possible.

Sensitivity analysis

Sensitivity analyses test the robustness of the results, identifying key experiments that have a high leverage, determining the number of extra trials needed in the case of inconclusive results and retrospectively testing for bias. In the case of Bayesian analysis, the sensitivity of the model to the choice of priors can be estimated. The results of the meta-analysis can be 'validated' using articles that become available after the literature search but before the end of the study; however, this will only be of limited value because of the specific nature of the additional articles (eg Prankel *et al* 2004).

Interpreting and reporting results

Meta-analysis reports should inform the reader on the study design, the potential of the experiments to be combined, the control of bias, the statistical analysis used, the sensitivity analysis used and the problems of application results (Moher *et al* 1999). The reporting of experimental results often merges into the methodology section because the research is not conducted in the traditional manner of experimental work followed by data analysis. A clear description of the key elements of each study is essential, including details of the origin of the data, sample size, the type of animal (species, breed, physiological state and age), the treatments applied and the outcomes. It is also important to state the criteria used for accepting or rejecting studies into the model. Often a description of the data is provided in tabular form. The limitation of space in printed journal publications may preclude the presentation of modelled responses of individual experiments; however, these should be provided in longer reports, for example, to the sponsors of the research. A forest plot can usefully portray the results of individual experiments (Figure 1), containing data on the mean, the size of individual studies (indicated by the size of the circle) and the credible intervals.

Interpretation of results should refer to the size and nature of the results of individual studies and any discrepancies discussed. Methodological limitations should also be discussed, for example, an inadequate dataset that is either too small or too varied. In addition, the consistency of the results should be considered in the context of the sensitivity analysis, as well as the need for further data.

Some applications of meta-analysis to animal science

Good practice is essential in conducting meta-analyses as the results may be considered more definitive than for individual studies. However, meta-analyses have sometimes been criticised for using inappropriate models, in particular linear models (eg Cole *et al* 2003) and reaching inappropriate conclusions. Meta-analysis has particular potential when variation between subjects is high; individual experiments may not have the necessary statistical power to produce significant results. For example, Jennions and Moller (2003) investigated whether the statistical power of individual studies was sufficient in behavioural ecology and animal behaviour papers to support the authors' conclusions. Of the 697 papers examined, Jennions and Moller estimated that only about 2%, 17% and 44% had the requisite power to statistically detect small, medium and large effects respectively, explaining 1%, 9% and 25% of the variance, respectively (Cohen 1988). Such is the power of meta-analysis, particularly in the eyes of funding agencies that want to be clear about results before implementing the research, that there have been calls for specific subject-orientated archives to be established to facilitate meta-analyses (Church 2002).

A review of the 130 papers found by the Web of Science search database, which included the words 'animal' and 'meta-analysis', determined that there have been 74 reports of meta-analyses involving animal experiments. Of these, 47 were conducted on experiments that involved animal models of human disease, 9 involved behavioural and psychological experiments, 7 evolutionary biology, 6 animal production and 5 veterinary science. Publications began with a modest number in 1993, and the number has increased significantly in the last five years to 27 per year by 2004. Papers published in the early years were characterised by meta-analysis of animal models of human disease, but later included mixed models, with animal experiments, and human and *in vitro* studies included, in addition to the subject areas identified above.

Three examples of meta-analysis in animal science

1. Simple models to combine experiments that determined the effects of underfeeding dairy cows on milk production and composition (Phillips 1991)

This research aimed to calculate the effect of a proportional reduction in herbage intake on the proportional change in milk yield, composition (protein content and milk energy output) and live weight change using published experiments with dairy cows fed predominantly on cut herbage. Proportional, rather than actual changes, were used because the latter were too dependent on circumstances. After analysing 34 published reports of mean experiment length 71 days, in which herbage was fed both *ad libitum* and at a proportion rate, it was found that the degree of restriction correlated positively with the reduction in milk yield, protein content, milk energy output (ME), ME^2 and ME × live weight. The ratio of change in ME to change in live weight was also related to the degree of restriction, so that at severe restrictions greater changes in milk production were observed than in live weight. A 10% reduction in herbage intake resulted in a 6%, 5% and 2% reduction in milk yield, fat yield and protein content, respectively.

The limitations of this study were, first, that each study contributed equally to the model, regardless of the number of animals and other factors that might be expected to affect the quality of the study. No weighting was possible on the basis of variance because the majority of the reports did not report this in any form, having been published in the 'grey literature' (publications that are not controlled by commercial publishing interests, eg newsletters, reports, working papers, theses, government documents, bulletins, fact sheets, conference proceedings, and other publications distributed free, available by subscription, or for sale). Second, no sensitivity analysis was conducted, so no confidence or credible intervals were made available. However, when the study was conducted in the 1980s, the science of meta-analysis was still in its infancy.

2. A meta-analysis of experiments that determined cadmium uptake in the liver and kidney of sheep (Prankel et al *2004, 2005)*

A random effects model was constructed to integrate the results of 21 controlled randomised trials in which sheep

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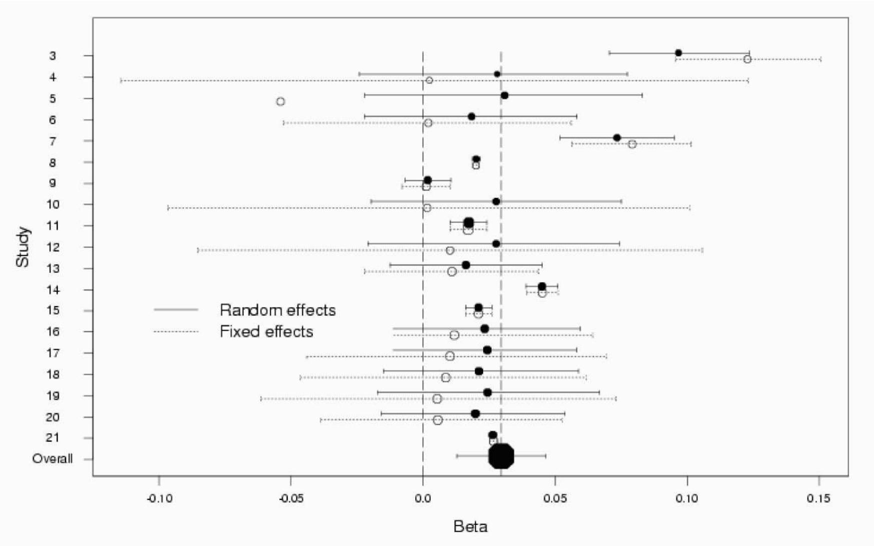
Figure 1



Meta-analysis of feeding trials using cadmium-enriched diets for sheep. Forest plot of the results for sheep kidney (Prankel *et al* 2004), illustrating values of beta (the accumulation coefficient over time) for each study and an overall value. For each study, the sample size is indicated by the size of the circle and the horizontal lines represent the credible intervals (95% probability that the value is within the two endpoints) for random and fixed effects models. Vertical dashed lines indicate the boundaries of the credible interval for the overall equation. Solid circles and continuous lines represent random effects model and open circles and dotted lines represent fixed effects. Studies 1 and 2 did not contain suitable data for the meta-analysis and were therefore not included in the forest plot.

Reprinted from *Environmental Research*, *94*, Prankel SH, Nixon RM and Phillips CJC, Meta-analysis of experiments investigating cadmium accumulation in the liver and kidney of sheep, 171-183. © (2005), with permission from Elsevier.

were fed diets with elevated cadmium concentrations. Cadmium concentrations in the livers and kidneys were then recorded after slaughter. The product of the cadmium concentration in the animal feed and the duration of exposure to that feed, were significant predictors of the cadmium concentration accumulated in liver and kidney. Accumulation also increased if the source of the cadmium in the animal feed was predominantly organic rather than inorganic. The researchers propose that the prime focus to decrease the risk of cadmium from animal origin adversely affecting human health should be preventing the livers and kidneys of older animals in polluted regions from entering the human food chain. Furthermore, the predictions of cadmium accumulation in sheep are applicable to a broad range of exposure situations and allow for the critical examination of cadmium accumulation in the human food chain.

An important feature of this meta-analysis was that it produced new information from between-experiment comparisons. Prior to this publication, there was no evidence of increased absorption of organically-bound cadmium, compared with inorganic forms, in any species as controlled experiments had not been conducted. Since that time, a controlled study has been conducted that verifies the results of the meta-analysis (Phillips *et al* 2005). Although the mechanism remains unclear, it is suspected that organically-bound forms interact less with antagonists in the intestine (Bailey *et al* 2001). A closely related element, zinc, is known to induce metallothionein production in the intestine, which aids absorption, but the affinity of cadmium for zinc metallothionein is believed to be low (Waales *et al* 1984).

3. A meta-analysis of experiments that included biochemical responses to underfeeding in cattle (Agenäs et al *2006 in press)*

Plasma concentrations of nutrient metabolites, such as glucose, urea, non-esterified fatty acids and ß-hydroxybutyrate, are commonly used to support prosecutions for the undernutrition of cattle in courts of law. A random effects meta-analysis of literature data for these metabolites in blood plasma was conducted against body condition score (BCS), body weight (BW) and changes in BCS and BW in cattle was conducted; 13 studies were included that contained data from animals that had been undernourished for more than 21 days. The credible intervals (meta-analysis equivalents of confidence intervals) of the gradients included zero for all regressions, showing that there were no significant relationships between any of the blood metabolites and BCS, BW or BWC. The results suggest that these metabolites are not suitable as evidence of long-term undernutrition.

Animal welfare implications

Meta-analysis of the existing literature allows conclusions to be made from a set of experiments that are more robust than subjective literature reviews, and should therefore, particularly in the case of conflicting results, reduce the number of animals required to undergo similar experiments. It is desirable for the details of relevant experiments to be controlled centrally, for example, by a central funding agency; however, it is recognised that the current *ad hoc*, multinational and competitive approach to animal research will reduce the likelihood of successfully achieving this goal. Alternatively, a provisional meta-analysis, conducted after a substantial body of work has been accomplished, will indicate how much further research is required to reach a definite conclusion. Meta-analysis also allows experimental design to be refined by narrowing the focus of the experiment toward relevant outcomes, possibly leading to fewer required procedures on animals. It is particularly suited to studies investigating responses where the frequency of response to treatment is low and the variability is high.

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