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A Systematic Review of Systematic Reviews and Meta-Analyses of Animal Experiments with Guidelines for Reporting

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To maximize the findings of animal experiments to inform likely health effects in humans, a thorough review and evaluation of the animal evidence is required. Systematic reviews and, where appropriate, meta-analyses have great potential in facilitating such an evaluation, making efficient use of the animal evidence while minimizing possible sources of bias. The extent to which systematic review and meta-analysis methods have been applied to evaluate animal experiments to inform human health is unknown. Using systematic review methods, we examine the extent and quality of systematic reviews and meta-analyses of in vivo animal experiments carried out to inform human health. We identified 103 articles meeting the inclusion criteria: 57 reported a systematic review, 29 a systematic review and a meta-analysis, and 17 reported a meta-analysis only. The use of these methods to evaluate animal evidence has increased over time. Although the reporting of systematic reviews is of adequate quality, the reporting of meta-analyses is poor. The inadequate reporting of meta-analyses observed here leads to questions on whether the most appropriate methods were used to maximize the use of the animal evidence to inform policy or decision-making. We recommend that guidelines proposed here be used to help improve the reporting of systematic reviews and meta-analyses of animal experiments. Further consideration of the use and methodological quality and reporting of such studies is needed.

Key Words: Animal experiments; Guidelines; Meta-analysis; Reporting; Review; Systematic review.

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INTRODUCTION

The use of animal experiments to inform human health interventions or policy is part of on-going debate,[1–3] with both ethical aspects of using animals in experiments and issues of relevance and extrapolation to humans being of concern. However, in many situations human evidence is lacking and so a thorough and critical evaluation of all the animal evidence is essential. Systematic reviews and, where appropriate, meta-analyses of animal experiments are advocated as a means of evaluating the relevant evidence to inform the likely human effect.[4–8] Systematic reviews offer a structured and transparent approach to searching for, reviewing and evaluating all available relevant evidence and so are directly relevant to the movement towards the 3Rs of animal research (replacement, reduction and refinement) (http://www.nc3rs.org.uk) and other initiatives on alternatives to animal experimentation (http://caat.jhsph.edu/). The increased precision of a meta-analysis over a single study,[6–8] in particular, has implications for reduction of animal research. For instance, rather than conduct a further experiment because none of the previous experiments have sufficient power, it may be appropriate to undertake a meta-analysis of the existing data.

Meta-analyses also offer the ability to explore consistency and generalizability of effects,[7] and a framework for investigation of (statistical, clinical and methodological) heterogeneity between studies and possible publication bias.[5,7,8] Through an understanding of sources of bias that may be apparent in primary studies, the quality of conducting and reporting animal experiments may be improved.[5,8]

So far, debate on the usefulness of systematic reviews and meta-analyses to evaluate animal experiments has focused on when such reviews are used to decide whether to commence clinical trials of an intervention in humans.[9] However, animal experiments usually form the basis of risk assessments for safe human exposure limits to chemical substances in the environment, in food and in commercial products. In such cases the available human evidence is often limited and results from animal experiments are the main source of evidence. Transparency regarding the various assumptions made, and identification and quantification of uncertainty in the resultant exposure limit estimates are essential for those involved in the review process and for professional users and "consumers" of the results alike. The potential for systematic reviews and meta-analyses to facilitate the evaluation of evidence for these risk assessments has been reported and discussed.[10–11]

It has been stated that 1 in 10000 animal studies in Medline were tagged 'meta-analysis,'[7] but the extent to which systematic reviews and meta-analyses have been used to evaluate animal experiments for human health effects, and their level of quality, is not known. In this paper we report findings of a systematic review of systematic reviews and meta-analyses of animal

experiments which were carried out to inform human health. We examine whether the reporting, and methods used, are of adequate quality to allow maximum use of the animal evidence to inform policy or decision-making.

METHODS AND MATERIALS

The strategies used to search medline (1966–July 2005), embase (1980–July 2005), toxline (1945–July 2005), ScienceDirect (1900–July 2005) and the grey literature broadly follow the Centre for Review and Dissemination's guidance on identifying systematic reviews and meta-analyses, including terms to identify animal experiments. Details are given on the internet (http://www.hs.le.ac.uk/division/epph/projects/epiandtox/). Further relevant articles were sought from the files of all authors. The reference lists of all identified relevant articles were assessed to identify further pertinent studies.

The following criteria were used to identify relevant systematic reviews and meta-analyses of animal experiments. For systematic reviews, details on the source(s) of evidence searched and some information on at least one of the following were sought,

i. Search terms used;
ii. Inclusion and exclusion criteria;
iii. Any limitations placed on the search.

For meta-analyses, a report of some form of quantitative synthesis of results of more than one experiment was required. Although uncommon for meta-analyses of human studies, a proportion of the meta-analyses identified in this paper did not use systematic review methods to identify the data for the meta-analysis. Regardless of whether a systematic review was used or not, all meta-analyses of animal experiments were sought.

Systematic reviews and/or meta-analyses were included if they involved in vivo animal experiments, where the purpose of reviewing animal evidence was to inform human health and where a medical intervention, an epidemiological association or effects of an exposure to a chemical substance was measured. Articles were considered relevant even if human evidence was sought in addition to the animal evidence.

RESULTS

One hundred and three articles were identified from the search strategies and met the inclusion criteria. Figure 1 details the number of studies identified at each stage of the searching process.

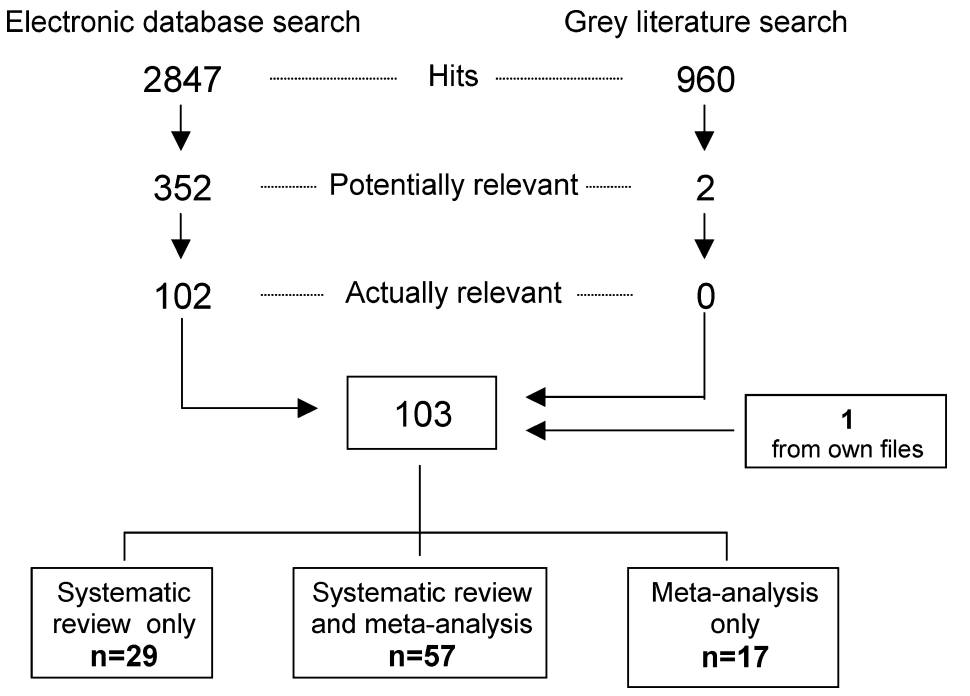

Figure 1: Flow chart of identified studies.

Fifty-seven articles report details of a systematic review only, 29 report a systematic review followed by a meta-analysis, and 17 report details of a meta-analysis only. A full list of these 103 articles can be found on the web (http://www.hs.le.ac.uk/division/epph/projects/epiandtox/). The settings for each systematic review or meta-analysis vary between these three groups. The majority of articles reporting only a systematic review evaluate a medical intervention (n = 48), as do those reporting a systematic review and meta-analysis (n = 23), but where only a meta-analysis is reported, the effect of an environmental chemical is the main setting (n = 10).

There has been a large increase in the last 10 years in the number of articles reporting systematic reviews and meta-analyses of animal experiments, particularly systematic reviews. Before 1996 only 13 articles reporting a systematic review and/or meta-analysis of animal experiments were published. Of the 90 articles published since the beginning of 1996, 54 have been reports of systematic reviews only.

Features of the Systematic Reviews

Of the 86 articles reporting the use of systematic review methods (57 systematic review only and 29 systematic review and meta-analysis), 52 articles report searching for both human and animal evidence to address the

research question of interest, but 34 consider the animal evidence only. Details of search strategies are generally given comprehensively in these systematic reviews: 73 out of the 86 articles report searching more than one source of evidence, usually electronic databases; Medline being the most common. Other electronic databases searched include Embase, Toxline, Current Contents and PsychLit. To supplement these electronic database searches, many articles also report searching conference and meeting proceedings and abstracts, searching the reference lists of relevant articles and the internet, or contacting authors, or companies for further (un)published data.

Features of the Meta-Analyses

Forty-six articles report the use of meta-analysis methods to combine animal experiments; 29 of these follow a systematic review, the other 17 articles review data obtained by a particular laboratory, or data on a set of replicate experiments. In many cases there are few details on the origin or identification of the primary data used in these meta-analyses. In addition, few of the meta-analyses report any assessment of the quality of the primary studies included in the meta-analysis.

Five of the 46 articles report the use of meta-analysis methods to combine human with animal data;[12–16] these are included in the review of meta-analysis methods. The number of experiments combined in each article varies from just three[9,17] to 397;[18] the median is 25, ignoring 5 meta-analyses which do not report the number of experiments being combined.

Individual summaries of the 46 meta-analysis articles, including the setting for the meta-analysis, the species/strain of animals included, the number of experiments included and some detail of the methods used (including effect estimates reported, whether and how heterogeneity was assessed, the synthesis methods used, any subgroup analyses, and whether and how publication bias was investigated) can be found at http://www.hs.le.ac.uk/division/epph/projects/epiandtox/.

Although simple methods for obtaining a quantitative synthesis across studies (e.g. calculating mean or median values) predominate, methods associated with meta-analyses of human randomized controlled trials (RCTs) (fixed and random effects precision-weighted models) are common, as are dose-response models. More specialized methods involve meta-analysis of diagnostic data using a summary receiver-operator characteristic (SROC) curve[19] and modelling distributions of p-values from multiple studies[18] (Fig. 2).

Between-study heterogeneity is a common feature in meta-analyses[20] and can have important implications for the synthesis and inference of a meta-analysis,[21] so must be addressed. Twelve of the 46 meta-analyses reviewed here make no reference to observing or assessing between-study heterogeneity. Of the 34 articles that do, 26 report assessing heterogeneity, but only 16

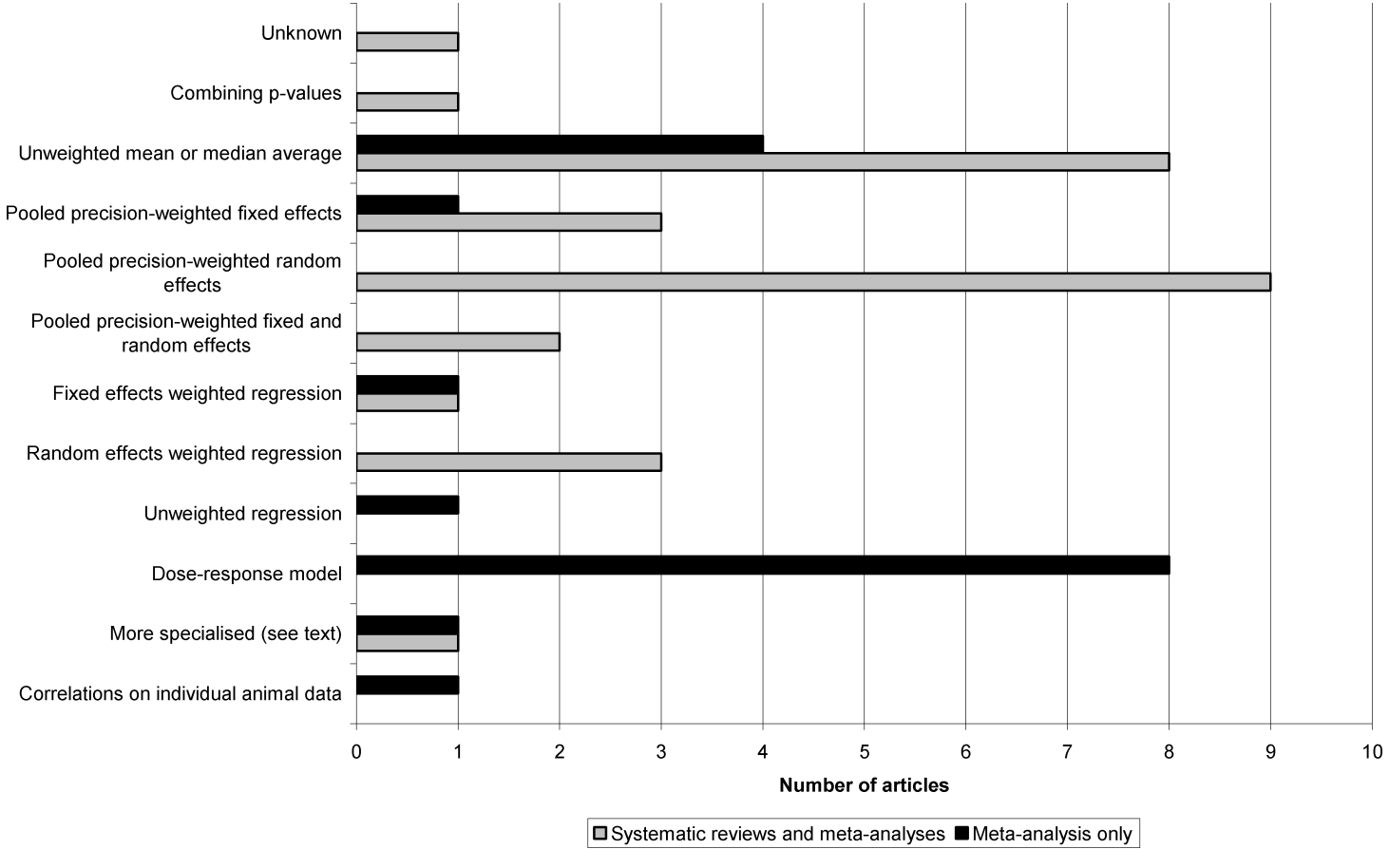

Figure 2: Methods of synthesis reported in 46 meta-analyses.

describe the methods used. When between-study heterogeneity is suspected (as in 21 of the 26 meta-analyses reporting an assessment of heterogeneity), it is dealt with in a number of ways. One meta-analysis ignores observed between-study heterogeneity stating there are too few studies to investigate sources of heterogeneity and four meta-analyses exclude the heterogeneous studies from further analysis. Of the remaining 16 meta-analyses suspecting between-study heterogeneity, 3 allow for it by reporting a random-effects estimate and 13 attempt to explain the heterogeneity through stratification and/or meta-regression.

A particular issue in meta-analyses of animal experiments is differences between animal species and strains. Seventeen of the 46 meta-analyses either failed to provide details on the species or strains used or gave no details on whether any differences were taken into account. Fourteen meta-analyses only included one species or strain of animal. Of the remaining 15 meta-analyses, five analysed different species separately and 10 took species differences into account using regression modelling.

Publication bias is another aspect that can significantly affect interpretation of a meta-analysis and is no less of an issue for animal experiments than for human studies. Only 17 meta-analyses identified in this review mention and consider, to some extent, publication bias. Assessment of publication bias is only reported in six of these: funnel plots, Egger's test[22] or the Failsafe number[23] are used. Two reasons were given for not assessing publication bias: that only a small number of studies are being reviewed[19] and that "the current statistical procedures addressing this issue lack validity."[24]

Although it is difficult to distinguish between poor execution and poor reporting of the systematic reviews and/or meta-analyses, there are, nevertheless, clear problems with the standard of quality of these articles, particularly the methods used. With the increase in use and publication of these methods, it is vital that an effort is made to improve the quality of reporting of meta-analyses of animal experiments and this is discussed further in the next section.

DEVELOPMENT AND APPLICATION OF GUIDELINES

Currently there are no guidelines for good quality reporting of meta-analyses of animal experiments. As a consequence of this systematic review guidelines based on the QUOROM (Quality of Reporting of Meta-analyses) statement,[25] but which also include features of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement[26] and further modifications making the guidelines specific to animal experiments have been developed. Although these guidelines are quite similar to QUOROM, they reflect the context of animal experiments and provide an initial step to improve the quality of meta-analyses of animal experiments. The proposed guidelines are given in Table 1.

Table 1: Proposed guidelines for the reporting of systematic reviews and meta-analyses of animal experiments.

Heading	Subheading	Descriptor
Title		Identify the report as a meta-analysis (or systematic review) of animal toxicology experiments
Abstract		
	Objectives	Use a structured format Describe explicitly the scientific question/ hypothesis
	Data sources	Describe the databases and other important information sources used
	Review methods	Describe the selection criteria (e.g. species, strain, intervention/exposure, outcome and study design): methods for validity assessment and data abstraction, the experiment characteristics, and quantitative data synthesis methods
	Results	Describe characteristics of the experiments included and excluded; qualitative and quantitative findings (e.g. point estimates and confidence intervals/ standard errors), stating clearly what is estimated: dose-response curves, LD50 etc; and subgroup analyses
	Conclusion	State the main results and their implications
Introduction		Describe the scientific problem explicitly, biological rationale for the intervention/exposure, and rationale for the review
Methods	Searching	Describe the information sources in detail (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), including keywords, search strategy and any restrictions (years considered, publication status, language of publication) Describe special efforts to include all available data (e.g. contact with authors, searching the grey literature)
	Selection	Describe the inclusion and exclusion criteria (defining intervention/exposure, principal outcomes, and experimental design) List excluded experiments and reasons for exclusion
	Validity and quality assessment	Describe the criteria and process used (e.g. blind assessments, quality assessment, and their findings)
	Data abstraction	Describe the process or processes used (e.g. completed independently, in duplicate), including details on reproducibility, inter-rate agreement. Whether aggregate data or individual animal data are abstracted

	Study characteristics	Describe the type of study designs, animals' characteristics (e.g. species, strain, age, sex), details of intervention/exposure (including route of administration, dose and duration), outcome definitions
	Quantitative data synthesis	Describe the principal measures of effect, method of combining results (e.g. fixed- and random-effects; meta-regression), handling of missing data; how statistical heterogeneity was assessed; how data from different species and strains were dealt with; adjustment for possible confounding variables; rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias—all in enough detail to allow replication
Results	Flow chart	Provide a meta-analysis profile summarizing experiment flow giving total number of experiments in the meta-analysis
	Study characteristics	Present descriptive data for each experiment (e.g. species, strain, age, sex, sample size, intervention/exposure, dose, duration)
	Quantitative data synthesis	Report agreement on the selection and validity of assessment and relevance to the scientific question/hypothesis; present simple summary results (e.g. forest plot); present data needed to calculate effect sizes and confidence intervals; identify sources of heterogeneity, impact of study quality and publication bias
Discussion		Summarize key findings; discuss scientific/clinical inferences and generalizability based on internal and external validity; interpret the results in light of the totality of available evidence, including data from human studies; discuss rationale for use of animal data to help inform human health outcomes; critically appraise potential biases in the review process (e.g. publication bias); suggest a future research agenda

Table 2: Results of quality assessments of meta-analyses of animal experiments and two sets of meta-analyses of human randomized controlled trials (RCTs).

	Percentage of meta-analyses fulfilling item		
Guideline item	**Toxicology meta-analyses (n = 46)**	**Hepatology meta-analyses[27] (n = 15)**	**Pharmacotherapy meta-analyses[28] (n = 32)**
Title—define as meta-analysis	59	93	22
Title—define as animal data[a]	52	—	—
Abstract—structured	29	40	50
Abstract—state objectives	98	73	69
Abstract—data sources	33	80	16
Abstract—review methods	2	20	9
Abstract—results	76	73	0
Abstract—conclusions	91	80	94
Introduction	100	100	91
Methods—information sources	74	87	59
Methods—special effort in searching[a]	13	—	—
Methods—inclusion/ exclusion criteria	67	73	56
Methods—list excluded studies[a]	7	—	—
Methods—validity	30	67	16
Methods—abstraction	50	87	22
Methods—characteristics	57	87	72
Methods—synthesis	63	100	69
Results—trial flow	35	47	6
Results—characteristics	52	87	81
Results—synthesis	41	57	75
Discussion	85	93	97

[a]Not an item in Quality of Reporting of Meta-analyses (QUOROM).

Each of the surveyed meta-analyses of animal experiments was assessed with reference to the items of the proposed guidelines. The findings (see Table 2) suggest that reporting of methods and results in the meta-analysis are particularly poor; so too are aspects of the abstract. The quality of reporting is worse in meta-analyses of environmental exposures than those looking at medical interventions (detailed results are given at http://www.hs.le.ac.uk/division/epph/projects/epiandtox/), although this can be partly explained by the fact that none of the environmental exposure meta-analyses are preceded by a systematic review. In a comparison with two sets of meta-analyses of human RCTs,[27,28] Table 2 shows that the meta-analyses of animal experiments are of a lower standard for elements of the methods, results and discussion sections.

RESULTS AND DISCUSSION

Systematic reviews and, where appropriate, meta-analyses of animal experiments have great potential in facilitating an evaluation of the evidence while keeping bias to a minimum. Moreover, although not reviewed here, meta-analyses have been used to inform the design of future animal experiments to help maximize relevance and extrapolation to humans,[29–31], and to synthesize both human and animal data.[32]

This review has found a number of deficiencies in the conduct and reporting of systematic reviews and meta-analyses of animal experiments which may have serious implications for decisions made on the basis of these reviews and for the use of these methods to evaluate animal evidence. However, the observation made in this paper that appropriate methods used in meta-analyses of human RCTs seem to have translated to meta-analyses of animal experiments on the efficacy of clinical interventions is promising. Adoption of systematic review and meta-analysis methods can be justified in terms of greater transparency of the process, worthwhile per se, but also for the potential it offers for better identification of missing evidence, and more appropriate identification of future study needs and designs. The extra cost of systematic review is small compared with potentially unnecessary costs (both financial and ethical) of inappropriate data collection, inefficient use of data, and unidentified uncertainty concerning the final products of the decision process—for example, the environmental exposure limits set—which may be associated with traditional approaches. The guidelines proposed here could help improve the future use of meta-analyses of animal experiments, especially those investigating environmental exposures and help to maximize the use of this information for human health care while contributing to the 3Rs of animal research.

However, the quality of primary studies is also crucial. There appear to be no widely used guidelines for the reporting of individual animal experiments. A whole issue of the ILAR journal (Institute for Laboratory Animal Research; Vol 43, No 3, 2002) is dedicated to giving guidance in the design and analysis of animal toxicology studies and an approach for evaluating the quality of toxicological studies has been proposed.[33] In the UK, the National Centre for the Replacement, Refinement and Reduction of Animals in Research is working towards improvements in experimental design (http://www.nc3rs.org.uk/) and guidelines for animal testing are also available from a number of U.S. and international organizations, such as the Center for Alternatives to Animal Testing (CAAT) based at the John Hopkins University (http://caat.jhsph.edu/) and the Organisation for Economic Co-operation and Development (OECD) (http://www.oecd.org/department/0,2688,en_2649_34377_1_1_1_1_1,00.html).

Initiatives to improve the reporting of the primary experiments should go hand-in-hand with both the conduct and reporting of systematic review and/or meta-analyses of animal experiments. In the interim, we recommend

that researchers use the guidelines presented with this paper (Table 1) during both the conduct and reporting of a systematic review and/or meta-analysis of animal experiments.

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