Reviewer's report

Title: Refining animal models in fracture research: seeking consensus for changing the agenda in optimising both animal welfare and scientific validity for appropriate biomedical use

Version: 1 Date: 30 January 2007

Reviewer: Jan van der Valk

Reviewer's report:

General
This is an interesting manuscript, drawing attention to the 3Rs in animal research in fracture research. It discusses the choice of animal models, choice of analgesia and termination criteria, and measures to improve harmonisation in study design between laboratories to improve comparison of data. The manuscript is a result of a forum discussion between experts in the field. Realising that it is difficult to summarise discussions in a manuscript I have to come to the conclusion that the paper is very extensive, arguments are repeated on several occasions, and needs some condensation.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
I suggest to combine parts of the introduction, the chapter on “defining a justified animal study” on page 7, the chapter on “the role of in vivo models in bone repair research” on page 17, and the chapter on “model standardisation” (pp 26), since all three chapters address similar issues with respect to the choice of animal model and therefore repeat each other.

Although the paper discusses the role of in vitro and computer-based studies in fracture research, it does not deal with the human patient as best study object and alternative to animal experiments. What opportunities do we have nowadays, or are we missing, to directly study fractures in men?

Pp3 halfway: “a database should be established to facilitate selection of anesthesia and pain management protocols”.
On http://altweb.jhsph.edu/ is a database on anesthesia and analgesia. Furthermore there is a large links section to links dealing with pain and distress (http://altweb.jhsph.edu/pain.htm). These should be mentioned.

PP5 last sentence 1st paragraph: The authors state “as the limitations and inaccuracies inherent in translating in vitro models results to in vivo equivalence”. The authors should substantiate this assumption, since this may be true in orthopaedic research, but is certainly not true in all research areas.

The same holds for the statement on pp7: “Many past and on-going research efforts seek to establish new and innovative approaches to in vitro modelling of in vivo complexity without clear progress or improved relevance”. The authors totally ignore recent progress. Although complex processes can yet not be totally replaced by in vitro methods, part of the results can be obtained by in vitro studies, although results have to be confirmed in in vivo studies.

PP29. Termination criteria. Termination criteria are also named “Humane endpoints”. For humane endpoints several reference sources are available:
• The CD Humane endpoints in laboratory animal experimentation (http://www.vet.uu.nl/nca/documents/humane_endpoints)
• Several links to humane endpoints sources (http://altweb.jhsph.edu/humane-endpoints.htm). These should be mentioned.

Conclusions: Although the authors spend many words on animal models, and urge to formulate appropriate selection criteria for animal models, this is not returned in the conclusions. This important recommendation should be listed as well.

I also miss the important recommendation that Termination criteria (Humane endpoints) should be defined before each animal study starts.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
PP8. (e.g., anti-inflammatory drugs, antibiotics\textsuperscript{19}, anti-cancer\textsuperscript{20} and anti-osteoporetic therapies\textsuperscript{21}. Missing closing bracket.

PP14. “(dogs, laboratory rats\textsuperscript{28,33,34}, horses\textsuperscript{35}, and lambs\textsuperscript{36}.” Missing closing bracket

PP20.”fractional power law, approximating (body mass)\textsuperscript{0.67}.” Delete brackets.

3rd sentence: replace “euthanazed” with “euthanized”.

Discretionary Revisions (which the author can choose to ignore)
From “defining a justified animal study” (pp7) it is not clear whether this deals with research animals in general or research animals in fracture research. In my opinion, it should focus on research animals in fracture research.

PP 11. In the chapter on anesthesia and pain management, I miss a discussion on proper anesthesia regime. The chapter focuses mainly on pain management.

PP23 and 26: the chapters on “fracture model standardisation” and “model standardisation” could be combined.

PP30, top sentence. Judgement of termination should be made by a veterinarian or qualified animal caretaker.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.