Pain management after surgery: are we good enough?

Eddie Clutton

The Wellcome Trust Critical Care Laboratory for Large Animals

Roslin Institute

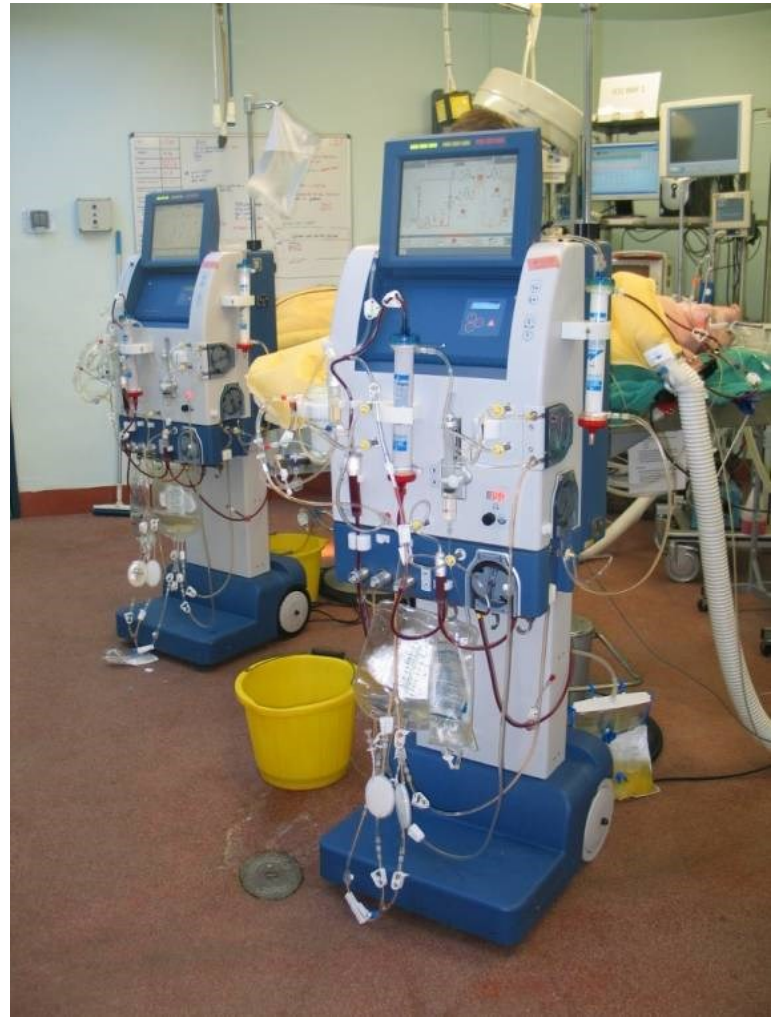
The University of Edinburgh

NORECOPA

June 2nd 2015

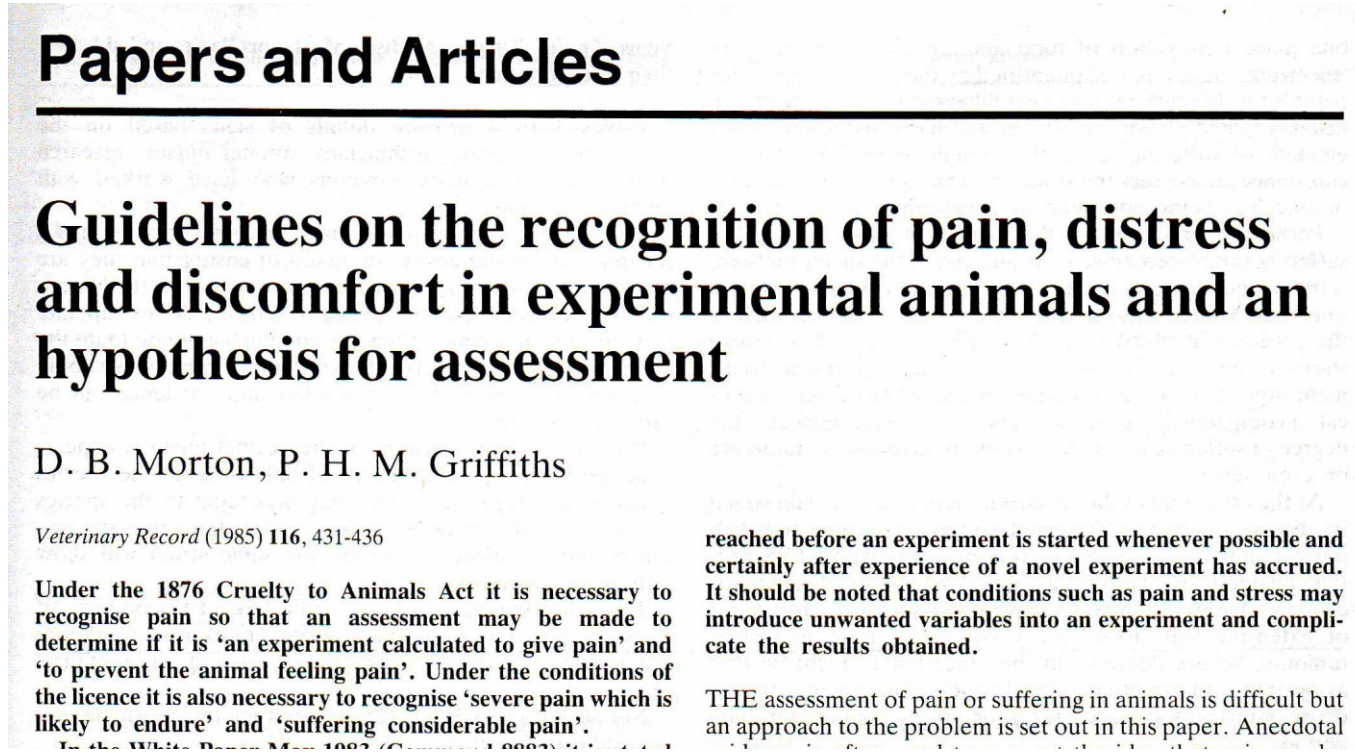
Wellcome Trust Critical Care Laboratory for Large Animals

- 4 bay intensive therapy unit
  - CT (& MRI?)
  - toxicology and pharmaceuticals
  - biotechnology
  - experimental surgery
  - pigs & sheep (poultry & cattle)
- Scientific director
- Operations director
- Clinical director (EC)
  - 24/5 (7) veterinary anaesthetic supervision
  - 3Rs observance (refinement)



postoperative pain management; importance?

- ethical
- justice
- legal
- practical
- medical



Papers and Articles

Guidelines on the recognition of pain, distress and discomfort in experimental animals and an hypothesis for assessment

D. B. Morton, P. H. M. Griffiths

Veterinary Record (1985) **116**, 431-436

Under the 1876 Cruelty to Animals Act it is necessary to recognise pain so that an assessment may be made to determine if it is 'an experiment calculated to give pain' and 'to prevent the animal feeling pain'. Under the conditions of the licence it is also necessary to recognise 'severe pain which is likely to endure' and 'suffering considerable pain'.

reached before an experiment is started whenever possible and certainly after experience of a novel experiment has accrued. It should be noted that conditions such as pain and stress may introduce unwanted variables into an experiment and complicate the results obtained.

THE assessment of pain or suffering in animals is difficult but an approach to the problem is set out in this paper. Anecdotal

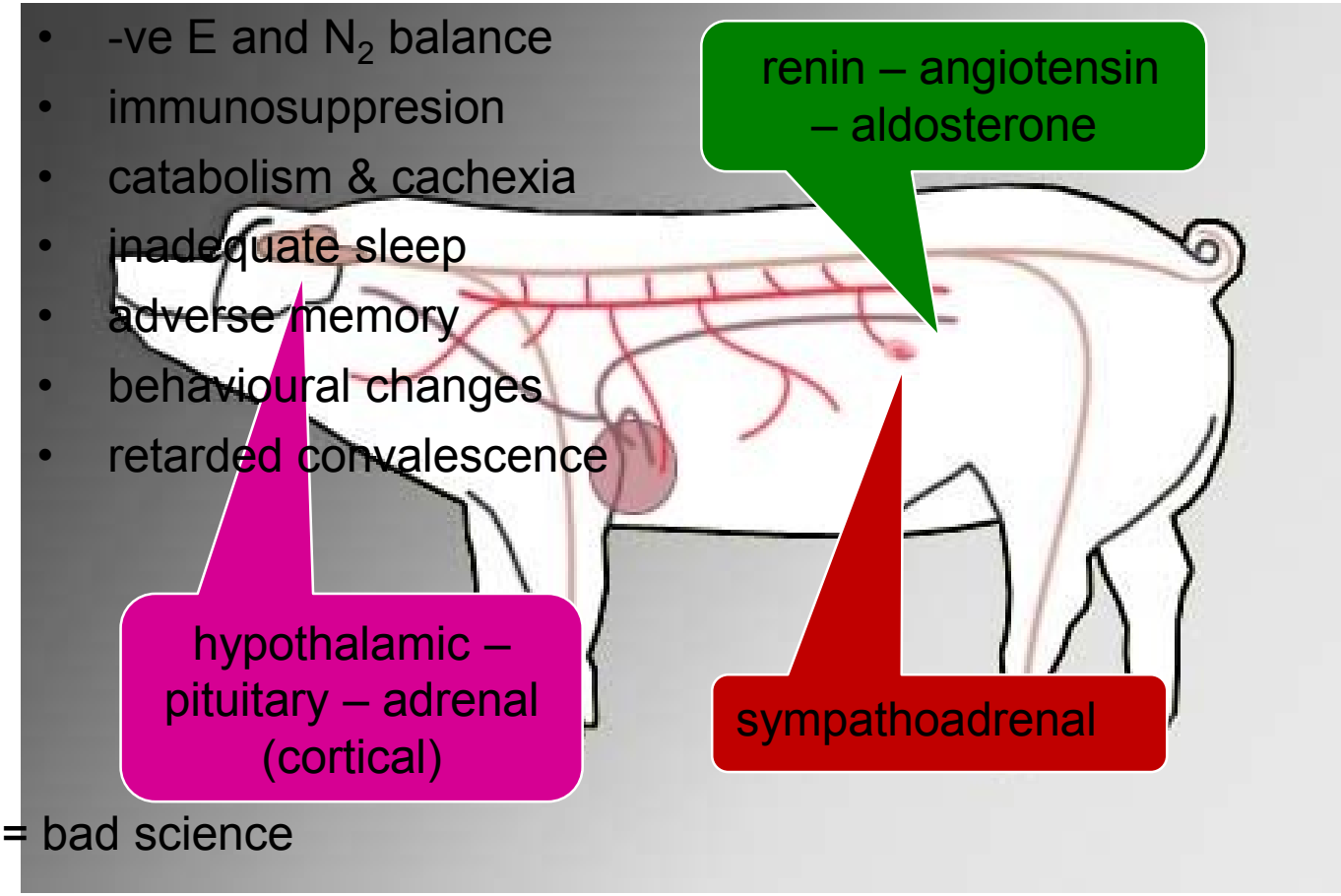
"pigs are a good model for human beings"

the *model* and the *modelled* must be treated similarly

postoperative pain management; importance?

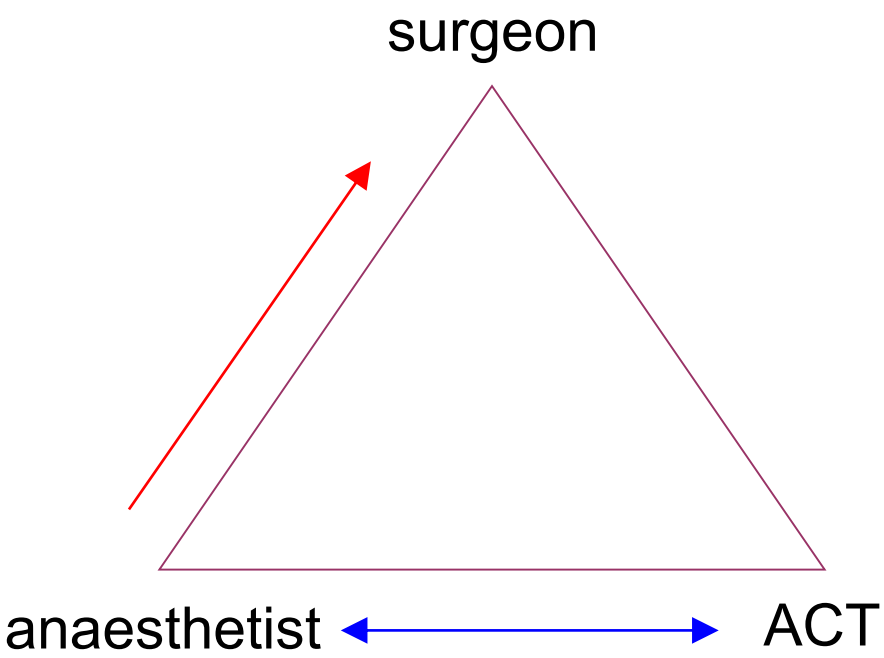
- ethical
- justice
- legal
- practical
- medical
- scientific
- social
- economic

- oliguria
- reduced appetite
- -ve E and N_2 balance
- immunosuppresion
- catabolism & cachexia
- inadequate sleep
- adverse memory
- behavioural changes
- retarded convalescence



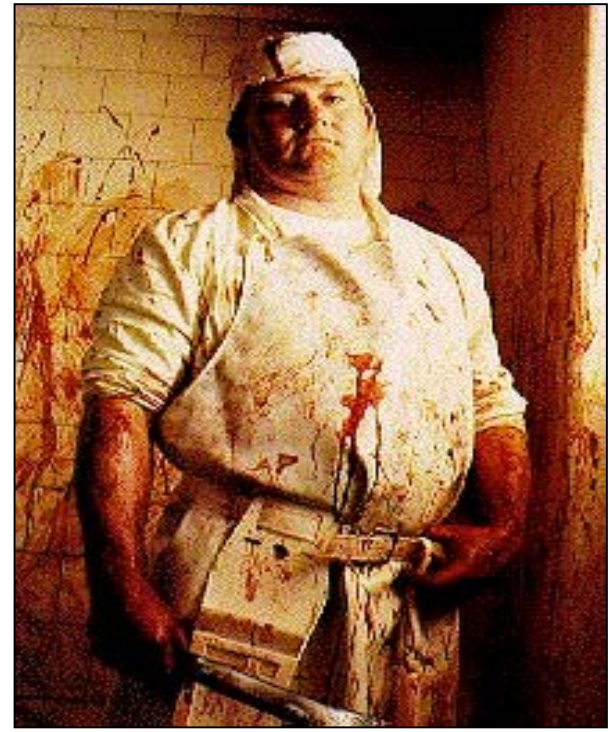
laboratory animal pain = bad science

are we doing enough? what is it?



are we doing enough? what is it?

- speed ◆ dexterity ◆ 0 traction ◆ minimal handling = minimal trauma
- *effective*ly fixing (bones [sternebrae])
- avoiding nerve damage
- low tension suturing
- “”splash” blocking
- wound infiltration – wound catheters
- local anaesthetic soaked swabs



what is postoperative pain management?

1) surgeon control

2) body position & physiotherapy

3. opioids
- NSAIDs
- local anaesthetics
- NMDA antagonists
- α_2 agonists
- antispasmodics
- mixed actions
- general anaesthetics
- SAIDs
- benzodiazepines
- anticonvulsants
- antidepressants

4) analgesic strategies
- pre-emptive analgesia
- polymodal pain therapy
- partial intravenous anaesthesia
- prolonged postoperative analgesia

what is postoperative pain management?

familiarisation (2 - 4 weeks)

feeding
watering
bedding
grooming
attention
(exercise
Dr Green)

morale

dressings & wound inspection

physiotherapy

pain recognition

pain quantification

reporting

analgesia

postoperative pain management

pain management after surgery: are we good enough?

?

preventative

management

staff
experience

anaesthesia

minimal
invasion

AWERB

TLC

pain
recognition


ELIZABETH II

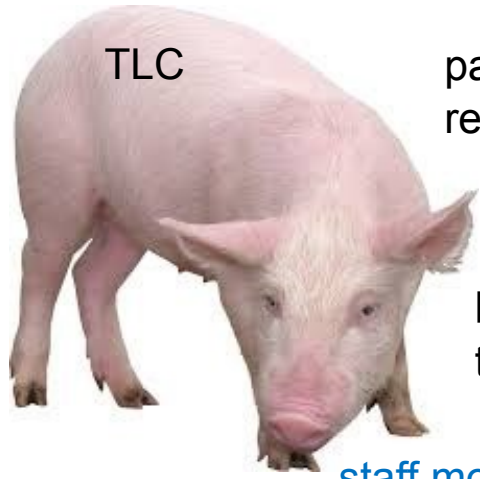
c. 14

Animals (Scientific
Procedures) Act 1986

1986 CHAPTER 14

An Act to make new provision for the protection of animals used for experimental or other scientific purposes. [20th May 1986]

BE IT ENACTED by the Queen's most Excellent Majesty, by and with the advice and consent of the Lords Spiritual and Temporal, and Commons, in this present Parliament assembled, and by the authority of the same, as follows:—



pain
treatment

staff motivation

quantifying

reduction

replacement

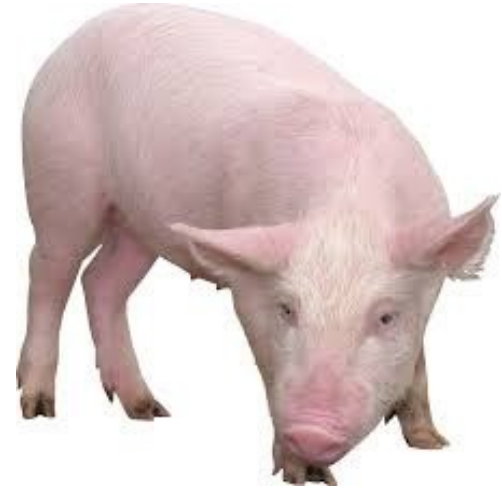
refinement ?

1) which component(s) ??

2) which level ??

pain management after surgery: are we good enough?

1. pig
   pain score & treat
   case reporting ??



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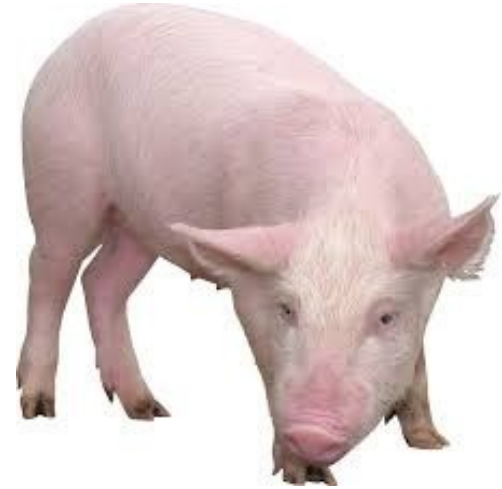
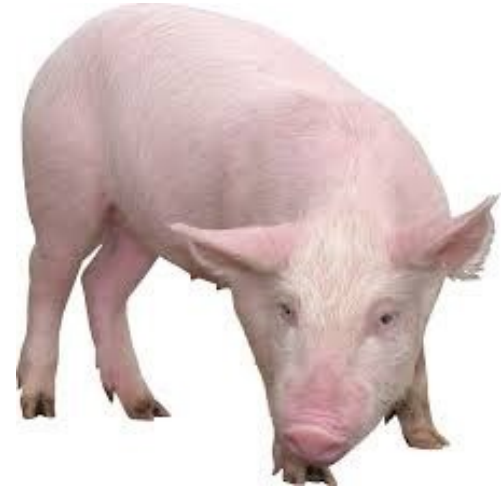
2. treatment group / study
   report pain scores & treatments *in study*
   ……study focus dependent

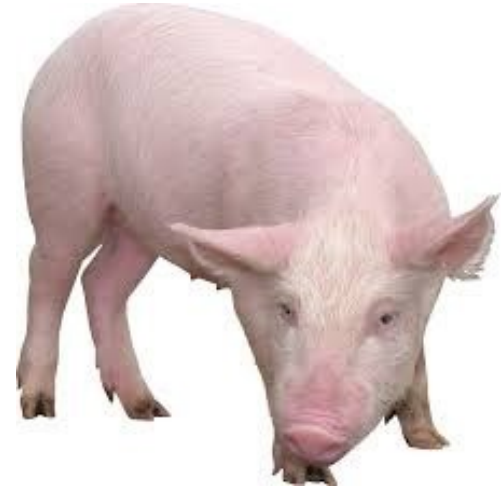


pain management after surgery: are we good enough?

3. laboratory / research group
   same argument
   refinement research focus

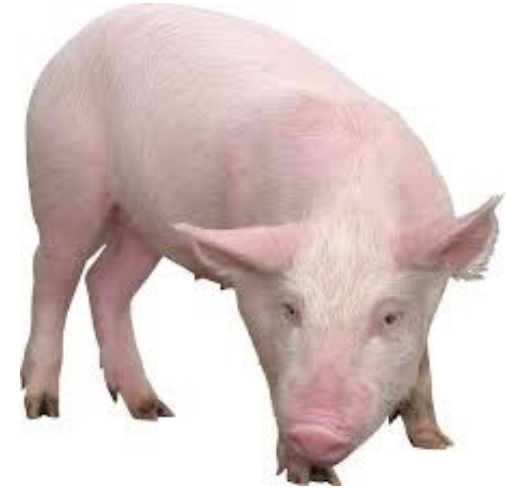


pain management after surgery: are we good enough?



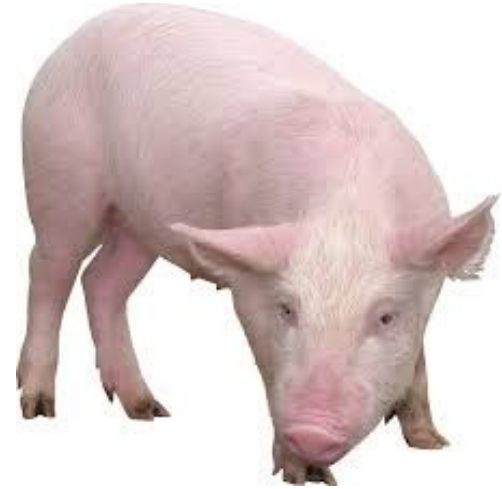
4. Institute
   HOI - PEL award

pain management after surgery: are we good enough?



5. National
   - any legislation?
   - quality of legislation?
     - species covered?
     - extent of detail ?
     - penalties?
   - refinement research
     - $budget
     - output
     - initiatives

pain management after surgery: are we good enough?

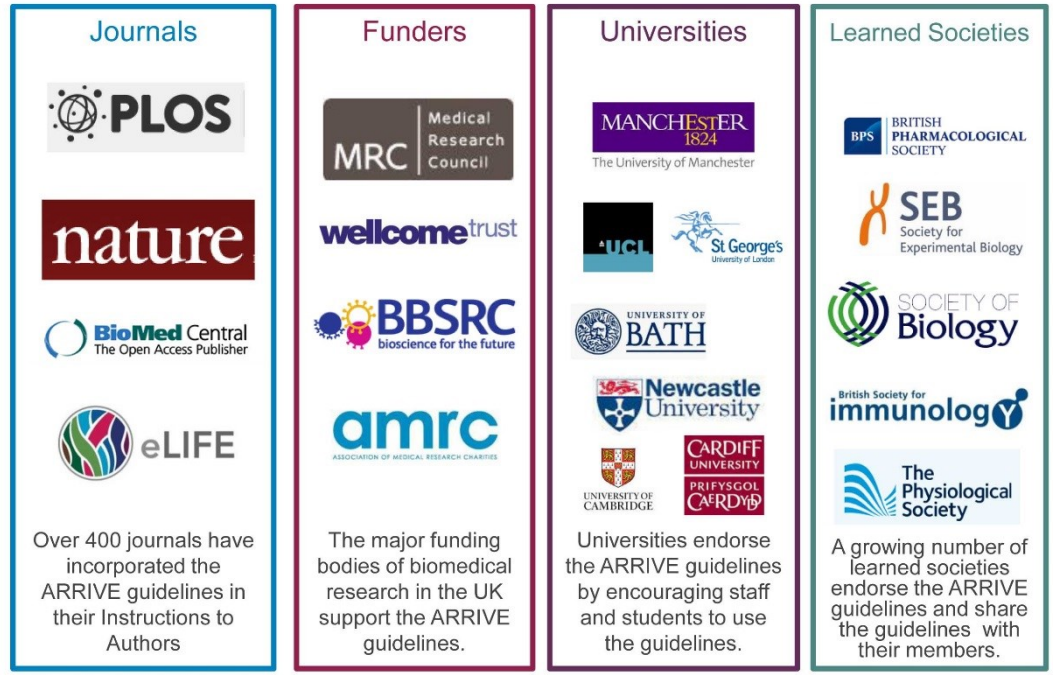


6. International
   publication based
   compliance with refinement guidelines (ARRIVE)

pain management after surgery: are we good enough?

ARRIVE

- (Animal Research: Reporting of *In Vivo* Experiments) guidelines
- 2010
- to improve the reporting of research using animals
- maximising information published
- minimising unnecessary studies
- subscription
- compliance (Journal)



	ITEM	RECOMMENDATION
Title	1	Provide as accurate and concise a description of the content of the article as possible.
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, meth thanasia). Provide details of any specialist equipment used, includ b. Wh
Experimental animals		
Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.
Sample size	10	pecify the total number of animals used in each experiment, and the number imals in each experimental group. plain how the number of animals was arrived at. Provide details of any sample
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).
Statistical methods	13	a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.
RESULTS		
Baseline data	14	For each experimental group, report relevant characteristics and health status of
Numbers		a. Give details of all important adverse events in each experimental group.
Outcomes and estimation	16	s for each analysis carried out, with a measure of precision (e.g. st or or confidence interval).
dverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.
ISCUSSION		
terpretation/ ientific implications	18	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results[2]. c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.
Generalisability/ translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.

Provide details of:

c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.

a. Give details of all important adverse events in each experimental group.

For each experiment and each experimental group, including controls, provide precise details of all procedures carried out.

For example:
a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).

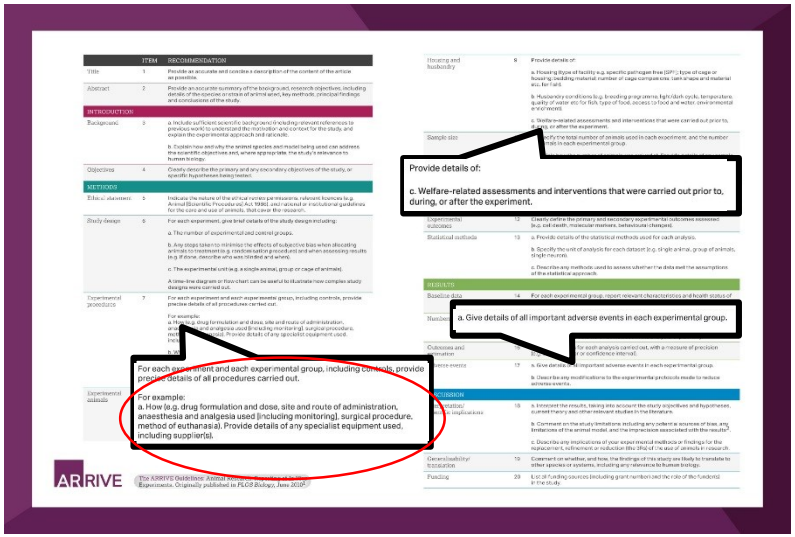
ARRIVE

The ARRIVE Guidelines: Animal Research: Reporting of *In Vivo* Experiments. Originally published in *PLOS Biology*, June 2010[1]

postoperative pain management

pain management after surgery: are we good enough?

select articles




Toxicology 294 (2012) 94–105

Contents lists available at SciVerse ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

A role for solvents in the toxicity of agricultural organophosphorus pesticides

Michael Eddleston[a,b,*], Jonathan M. Street[a], Ian Self[c], Adrian Thompson[a], Tim King[e], Nicola Williams[f], Gregorio Naredo[g], Kosala Dissanayake[a], Ly-Mee Yu[f], Franz Worek[h], Harald John[h], Sionagh Smith[d], Horst Thiermann[h], John B. Harris[i], R. Eddie Clutton[c]

ARTICLE INFO

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Solvents
Cyclohexanone

ABSTRACT

Organophosphorus (OP) insecticide self poisoning is responsible for about one quarter of global suicides. Treatment focuses on the fact that OP compounds inhibit acetylcholinesterase (AChE); however, AChE-reactivating drugs do not benefit poisoned humans. We therefore studied the role of solvent cofomulants in OP toxicity in a novel minipig model of agricultural OP poisoning. Gottingen minipigs were orally poisoned with clinically relevant doses of agricultural emulsifiable concentrate (EC) dimethoate, dimethoate active ingredient (AI) alone, or solvents. Cardiorespiratory physiology and neuromuscular (NMJ) function, blood AChE activity, and arterial lactate concentration were monitored for 12 h to assess poisoning severity. Poisoning with agricultural dimethoate EC40, but not saline, caused respiratory arrest within 30 min, severe distributive shock and NMJ dysfunction, that was similar to human poisoning. Mean arterial lactate rose to 15.6 [SD 2.8] mM in poisoned pigs compared to 1.4 [0.4] in controls. Moderate toxicity resulted from poisoning with dimethoate AI alone, or the major solvent cyclohexanone. Combining dimethoate with cyclohexanone reproduced severe poisoning characteristic of agricultural dimethoate EC poisoning. A formulation without cyclohexanone showed less mammalian toxicity. These results indicate that solvents play a crucial role in dimethoate toxicity. Regulatory assessment of pesticide toxicity should include solvents as well as the AIs which currently dominate the assessment. Reformulation of OP insecticides to ensure that the agricultural product has lower mammalian toxicity could result in fewer deaths after suicidal ingestion and rapidly reduce global suicide rates.

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1. Introduction

Pesticides are used extensively in tropical agriculture to increase crop yield (World Health Organization, 1990). However, this use has a cost: pesticide self-poisoning is a major public health problem (Jeyaratnam, 1990; Eddleston and Phillips, 2004), killing at least 250–370,000 people every year (Gunnell et al., 2007a). Organophosphorus (OP) insecticides, acting as acetylcholinesterase (AChE) inhibitors, are the most important, being responsible for more than 2/3 of deaths due to their high toxicity and widespread use (Eddleston, 2000). Medical treatment is difficult, with case fatality often over 20% (Eddleston, 2000). We recently found that the specific antidote, the AChE reactivator pralidoxime, offers little benefit to patients severely poisoned with Environmental Protection Agency (EPA)/World Health Organization (WHO) Class II 'moderately toxic' OP insecticides (Eddleston et al., 2009a; Buckley et al., 2011). This suggests that other components of the agricultural OP formulations might be necessary for acute toxicity.

Although toxicity from coformulants is recognised for glyphosate herbicides (Bradberry et al., 2004), their role in the acute mammalian toxicity of the emulsifiable concentrate (EC) insecticide formulations used in agriculture and ingested in self-harm has been explored only once (Casida and Sanderson, 1961) and then apparently forgotten. Medical textbooks do not consider coformulants to be a clinical issue in OP insecticide poisoning. Of

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inclusion + exclusion
species
dates
procedures

analyse

generate metrics

postoperative pain management

are we good enough?

ATLA 33, 119–127, 2005

Anaesthesia and Post-operative Analgesia Following Experimental Surgery in Laboratory Rodents: Are We Making Progress?

Claire A. Richardson and Paul A. Flecknell

Comparative Biology Centre, University of Newcastle, Newcastle-upon-Tyne, UK

- structured reviews
- peer-reviewed journals
  - anaesthetics & analgesics*
  - painful procedures
  - laboratory rodents
  - (1990 – 1992) – (2000 – 2002)**

- skin incision
- craniotomy
- laparoscopy
- burning (skin)
- laparotomy
- orthopaedics
- thoracotomy

- written *vs* reported analgesic rate increased 2.7 – 19.8%
- *"the overall level of post-operative pain relief for laboratory rodents is still low"*

*timing unspecified, *in articles describing anaesthetics & analgesics*

**follow up

postoperative pain management

are we good enough?

- structured reviews
- peer-reviewed journals
  - analgesics*
  - painful procedures
  - rabbits, pigs, sheep, dogs, NHPs
  - (2000 – 2001) – (2005 – 2006)*

- reported analgesic rate increased 50 – 63%

Original Article

Reported analgesic administration to rabbits, pigs, sheep, dogs and non-human primates undergoing experimental surgical procedures

C A Coulter, P A Flecknell and C A Richardson

Comparative Biology Centre, Medical School, Framlington Place, Newcastle University, Newcastle upon Tyne NE2 4HH, UK
Corresponding author: Claire A Richardson. Email: Claire.Richardson@ncl.ac.uk

Laboratory Animals 2009; **43**: 232–238. DOI: 10.1258/la.2008.008021

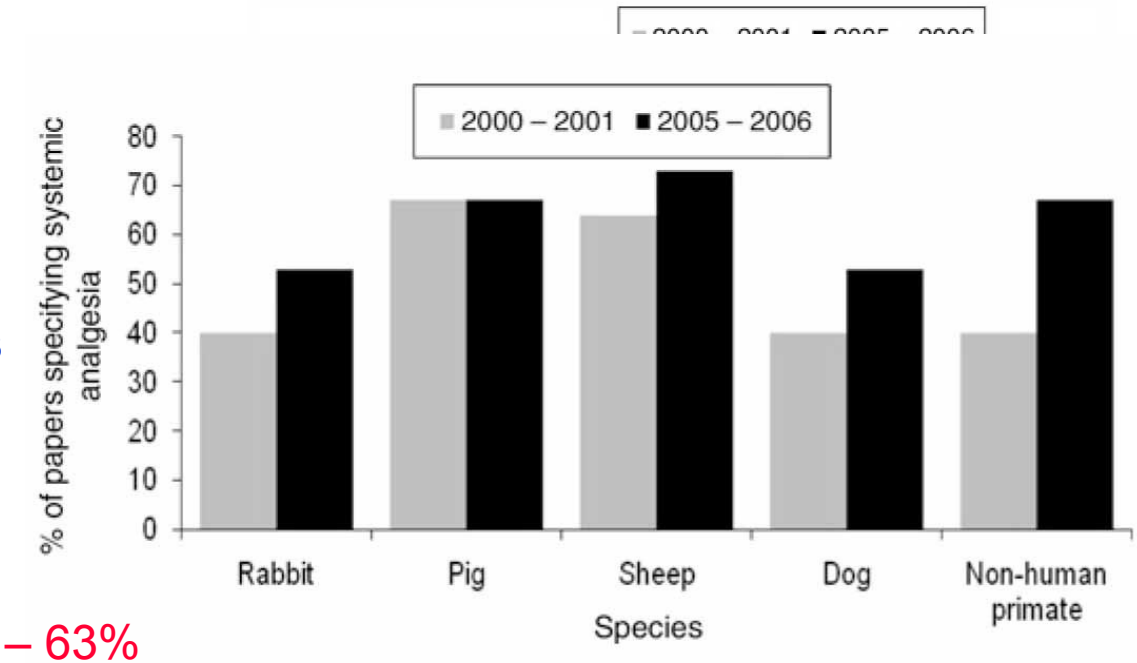


Figure 1 Reported systemic analgesic administration classified by species

- *"Overall, (large animals) were more likely to receive analgesics following potentially painful experimental procedures than laboratory rodents.....analgesic administration to 'large' laboratory species is still not optimal.*

postoperative pain management

are we good enough?

Coulter *et al. BMC Veterinary Research* 2011, **7**:12
http://www.biomedcentral.com/1746-6148/7/12

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Reported analgesic administration to rabbits undergoing experimental surgical procedures

Claire A Coulter, Paul A Flecknell, Matthew C Leach, Claire A Richardson*

- structured reviews
- peer-reviewed journals
  - analgesics*
  - the *same* painful procedures
  - rabbits
  - (1995 – 1997) – (2005 – 2007)

- reported analgesic rate increased 16% – 20%
- AWERB approval α analgesic use ($p<0.001$)

- *"whilst analgesic use is increasing, rabbits do not always receive analgesia when they undergo experimental surgery."*

postoperative pain management

are we good enough?

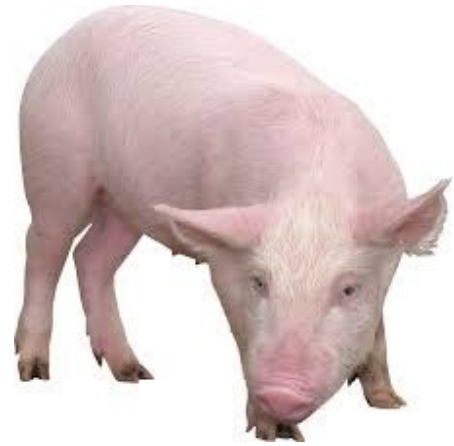
Pain management in pigs undergoing experimental surgery

Guen Bradbury, Michael Eddleston, Eddie Clutton.

The Wellcome Trust Critical Care Laboratory for Large Animals
Roslin Institute
The University of Edinburgh

RSPCA / AHVLA
September 19th 2014

- structured review
- peer-reviewed journal
  - the *same* painful procedures
  - pigs
  - 2012 – 2014
  - analgesics* AND *all aspects* of pain management
  - identify *intent* to *refine*



*timing and purpose specified; *in all papers describing painful surgery*

are we good enough?

of 233 articles describing painful (human) procedures in pigs.....

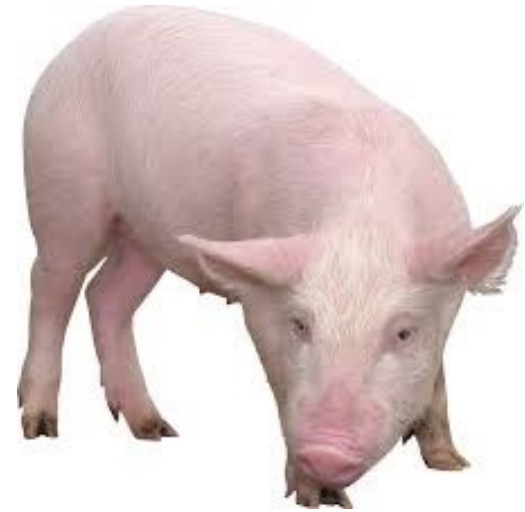
83% describe use of drugs with analgesic properties

37% described drug prescription for post-operative analgesia

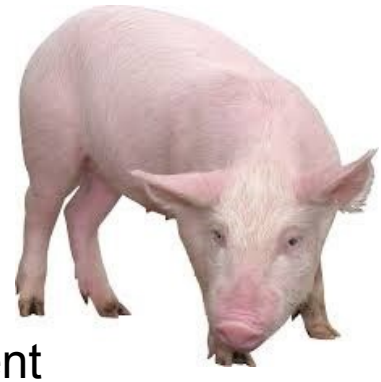
no article justified choice

10% described postoperative pain assessment

1 used a pain scoring system



pain management after surgery: are we good enough?



- reported ≠ actualité ?
- omission
  - oversight
  - detail considered; considered unnecessary
  - author not anaesthetist (unawareness)
  - editorial restrictions (word counts)
- follow-up studies (X2)
  - reported = actualité
  - not good enough at post-operative pain management
  - unconvincing intent to refine
  - formalised techniques to quantify refinement
  - *Nature* : on-line *detailed* methodologies

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SEVENTH FRAMEWORK PROGRAMME