How the AWB can help with reproducibility

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RSPCA RESEARCH ANIMALS DEPARTMENT
RSPCA Research Animals Department works to:

- Promote replacement, reductions in numbers and suffering, and improvements in welfare while animal use continues
- Ensure that ethical issues are raised and addressed
- Promote critical and open harm-benefit analysis of animal use
  - reproducibility is critically important, as it directly impacts on benefit
Four key RSPCA work areas ...

- **Severe suffering** project, with LASA, LAVA and IAT (here)
- Promoting **effective regulation**, UK and internationally
- **Getting more welfare and ethics** into education and training
- Work to promote effective **ethics committees** and **Animal Welfare Bodies (AWBs)**
Why the AWB is a good thing

BENEFITS FOR ANIMALS, SCIENCE AND STAFF, AS SET OUT IN EC WORKING DOCUMENT (HERE)

- Provides motivation and support for animal welfare and the Three Rs
- Provides advice on the project application process
- Improves communication between scientists and animal technologists
- Fosters a good culture of care
- Improves public confidence in the quality of scientific work and care
- Improves the quality of science ...
Pooling of Animal Experimental Data Reveals Influence of Study Design and Publication Bias
Malcolm R. Macleod, PhD; Tori O’Collins, BSc; David W. Howells, PhD; Geoffrey A. Donnan, MD

A call for transparent reporting to optimize the predictive value of preclinical research
Story C. Landl1, Stuart G. Amar1, Khypna Asadullah1, Christ P. Austin1, Robin Blumenstein1, Eileen W. Bradley1, Ronald G. Crystal1, Robert B. Darrat1, Robert J. Ferrante1, Howard Ellis1, Robert Finkelstein1, Marc Fisher1, Howard E. Gelbermann1, Robert M. Gold1, John L. Goodridge1, Robert A. Gross1, Amelie K. Guthrie1, Sharon E. Hendershot1, David W. Howells1, John Hagan1, Katrina Kimber1, Walter Knobler2, Dimitri Kraus1, Stanley E. Lapidus1, Michael S. Leshner2, Malcolm R. Macleod1, John M. McCall1, Richard T. Mosley3,5, Kalyani Narasimhan1, Linda J. Noble1, Steve Pearson1, John D. Porter1, Oswald Steward1, Ellis Ungar1, Ursula Utz1 & Shuli D. Silverberg1

Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases
Konstantinos K. Tsilidisi1,6, Orestis A. Panagiotou1,6, Emily S. Sena2,3, Eleni Aretouli4,5, Evangelos Evangelou1, David W. Howells3, Rustam Al-Shahi Salman2, Malcolm R. Macleod2, John P. A. Ioannidis6

Lost in Translation
Bumps in the Road Between Bench and Bedside
Leonard A. Levin, MD, PhD
Helen Y. Danesh-Meyer, FRANZCO

Research in Translation
Can Animal Models of Disease Reliably Inform Human Studies?
H. Bart van der Worp1,2, David W. Howells3, Emily S. Sena2,3, Michelle J. Porritt3, Sarah Rewell2, Victoria O’Collins2, Malcolm R. Macleod3

... which is critically important given current issues with reproducibility
Many issues with reproducibility could be resolved with the application of empathy and resources

- This would minimise confounds associated with unrelieved pain and avoidable distress; prevent data being lost due to mortality
- The AWB’s task list effectively covers all this (and experimental design) – *if properly implemented*
- Vets can do a lot to help support the AWB and can also use the AWB to channel their concerns
<table>
<thead>
<tr>
<th>Mice and rats are ...</th>
<th>... but</th>
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<tbody>
<tr>
<td>Nocturnal and crepuscular</td>
<td>they are housed in bright light and used during the day when they would normally be sleeping</td>
</tr>
<tr>
<td>Highly dependent on smell and scent markings</td>
<td>their markings are completely destroyed whenever the cage is cleaned</td>
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<tr>
<td>Made extremely anxious when captured by the tail (mice)</td>
<td>most people catch them by the base of the tail</td>
</tr>
<tr>
<td>Most comfortable at a temperature of 26 to 34 °C (mice)</td>
<td>many facilities house them at colder temperatures, and/or do not provide sufficient nesting material</td>
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Photos: Jane Hurst, Liverpool University
And better welfare = better science

Example: amyloid plaques

- $\text{APP}^\text{Swe}/\text{PS}\text{1}_{166P}$ mice group housed in ‘standard’ conditions or 80x50x80 cm cage with several floors, wheels, refuges
- Enrichment transiently accelerated amyloid deposition but had protective effect on cognitive deterioration

Montarolo F et al. (2013) PLoS ONE 8(7): e69381
Author’s analysis of these data

- Environmental factors can modulate symptoms and pathological progression in APP$^{\text{Swe/PS1}}$$_{166P}$ mice
- Confirmed dissociation between amyloid burden and cognitive deterioration, as in human patients
- Reviewed and discussed other studies with different EE protocols – using enrichment as a tool to help understand effects of environment on pathology

For further information and examples see [here](#)
Tasks of the AWB - 1

DIRECTIVE ARTICLE 27

(a) advise the staff dealing with animals on matters related to the welfare of animals, in relation to their acquisition, accommodation, care and use;

(b) advise the staff on the application of the requirement of replacement, reduction and refinement, and keep it informed of technical and scientific developments concerning the application of that requirement;

(c) establish and review internal operational processes as regards monitoring, reporting and follow-up in relation to the welfare of animals housed or used in the establishment;
(d) **follow the development and outcome** of projects, taking into account the effect on the animals used, and identify and advise as regards **elements that further contribute to replacement, reduction and refinement**; and

(e) advise on **rehoming** schemes, including the appropriate socialisation of the animals to be rehomed.
A point to note

• The AWB does not perform project evaluation - that is done by the competent authority

• ... but the AWB’s advice can help to ensure that proposed projects are justifiable, reproducible and conducted according to good practice
How do the AWB’s tasks facilitate reproducibility, and how can the veterinarian contribute to the AWB?
The Animal Welfare Body

ARTICLE 26

The animal-welfare body shall include at least the person or persons responsible for the welfare and care of the animals and, in the case of a user, a scientific member. The animal-welfare body shall also receive input from the designated veterinarian (or the expert referred to in Article 25)
IN INVOLVING A WIDER MEMBERSHIP

Although the membership of the AWB does not require a veterinarian, their input is required under the Directive as it is considered to be very valuable. Therefore a number of Member States have mandated their formal inclusion in their AWBs.

**UK ASPA:** The NVS should be an active member of, and play a central role in, the AWERB at your establishment. (Note: At least one NVS at the establishment must be a full member of the AWERB.)
Tasks of the AWB - 1

ARTICLE 27

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(b) advise the staff on the application of the requirement of replacement, reduction and refinement, and keep it informed of technical and scientific developments concerning the application of that requirement;

(c) establish and review internal operational processes as regards monitoring, reporting and follow-up in relation to the welfare of animals housed or used in the establishment;
EC guidance on task (a)

- AWB **should be the forum** at which new or revised practices relating to animal care and use can be considered and endorsed
- Developing local policies and standards including SOPs
  - refined admin and sampling; severity assessment; environmental enrichment
  - dealing with exceptions to SOPs (e.g. single housing)
- Disseminating information on standards and policies
  - standing agenda items, e.g. health reports from veterinarian
ARTICLE 27

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EC guidance on task (b)

- Development of and input into guidance on application of the Three Rs for inclusion in the Education and Training Framework, including CPD
- Identification and dissemination on good practice on the Three Rs e.g. improvement of experimental design and optimisation of group sizes
- Ensuring Reduction and Replacement are specifically addressed ... members with expertise in experimental design and developments in alternatives ...
Tasks of the AWB

ARTICLE 27

(a) advise the staff dealing with animals on matters related to the welfare of animals, in relation to their acquisition, accommodation, care and use;

(b) advise the staff on the application of the requirement of replacement, reduction and refinement, and keep it informed of technical and scientific developments concerning the application of that requirement;

(c) establish and review internal operational processes as regards monitoring, reporting and follow-up in relation to the welfare of animals housed or used in the establishment;
EC guidance on task (c)

• Reviewing the effectiveness of systems in place to ensure that animals are adequately monitored
  – day to day monitoring cageside
  – observing and recording behaviour and clinical signs
  – using EC Working Document on Severity Assessment, including a ‘team approach’
(d) follow the development and outcome of projects, taking into account the effect on the animals used, and identify and advise as regards elements that further contribute to replacement, reduction and refinement; and

(e) advise on rehoming schemes, including the appropriate socialisation of the animals to be rehomed.
EC guidance on task (d)

- Input at project planning and application stage can improve the quality of applications, ensure Three Rs implemented and check whether there are suitable facilities and expertise on site
- Mid-term project reviews can ensure projects are on track and identify Three Rs opportunities
- AWBs can work with project holders to tailor severity assessment
Three ways that vets can enhance the AWB

Photo: RSPCA
1. Understanding biology and behaviour

- Scientists are experts in their field, but many could learn more about their study species.

- Veterinary expertise can improve the AWB’s advice on ‘matters relating to the welfare of animals’, ‘refinement’, and ‘technical and scientific developments’.

- This will reduce confounds due to animals being unable to express physiological and ethological needs.
2. Understanding harms to animals, and how to assess and alleviate these

- Vets can help to shift the AWB’s thinking away from ‘what will be done to the animal’ to ‘what will the animal experience?’
- Especially important for species where behaviour is difficult to interpret, or for cumulative severity
- Veterinary input into recognising, assessing and alleviating suffering is invaluable
- This aids reproducibility by reducing confounds associated with unrelieved pain, or psychological distress
3. Being an advocate for animals, including supporting animal technologists and lay members

- A specific perspective, to help ensure that the full spectrum of knowledge and opinion is included
- Vets have the authority to help other AWB members join discussions with confidence
- There may be an expectation that the vet will be a ‘champion’ for animals and ‘make people think’ (see tinyurl.com/ygmcha27)
- Leadership skills, ability to influence and understanding of collective responsibility are all important for the AWB
National Committees

ARTICLE 49

- Advise competent authorities and AWBs on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practice

- Exchange information on the operation of AWBs and project evaluation and share best practice throughout the Union
Vets can help by supporting:

- Local AWBs
- Their National Committees (if they exist)
- National AWB networks, e.g. Netherlands, Belgium, UK
- Culture of Care network (see https://norecopa.no/alternatives/culture-of-care)
Take home messages …

• Thoughtful and robust implementation of the AWB’s tasks would significantly help to solve the reproducibility crisis
• Take another look at the EC Working Document on AWBs and NCs
• You may like to reflect on your level of input into the AWB as a veterinarian, and how much support you receive
• If you want to become more involved, could you get further support from the ‘person responsible for ensuring compliance’, or ESLAV and ECLAM?