The **ASC**

Animals in Science Committee

Chair: Dr John Landers
Secretary: Caroline Wheeler
14th Floor Lunar House
40 Wellesley Road, Croydon, CR9 2 BY
Email:asc.secretariat@homeoffice.gsi.gov.uk
ASC Secretariat tel: 020 8196 4414

Baroness Williams of Trafford

24 May 2018

Dear Minister,

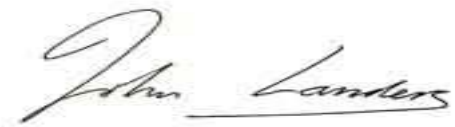
Review of harm-benefit analysis in the use of animals in research: Recommendations for ASRU

I wrote to you on 21 November 2017 to present the findings of the Animals in Science Committee (ASC) Report "Review of harm-benefit analysis in the use of animals in research".

The report, which was a comprehensive review of the harm-benefit analysis procedure, sets out twenty-seven recommendations for strengthening the legitimacy of harm benefit analysis and for promoting its further development. Since then, members of the ASC have considered which of those recommendations might fall to ASRU to implement and these are set out below.

I look forward to hearing, in due course, how these recommendations have been implemented.

Yours sincerely,



Dr John Lander
Chair, Animals in Science Committee

Review Of Harm-Benefit Analysis In The Use Of Animals In Research

Summary of recommended actions for ASRU. The Review of the Harm-Benefit Analysis (HBA), carried out by the Animals in Science Committee, specifies and justifies twenty-seven recommendations[1] for strengthening the legitimacy of the HBA and for promoting its further development. Many of these recommendations fall within the remit of ASRU and are included below for action. The process of HBA and related ASRU interventions is illustrated in Figure 1.

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1. Assessing Harms Experienced By Animals

Recommended Action 1 [from Report Recommendations 1 & 4]:

Data on prospective severity and predicted adverse effects, including cumulative suffering, should be collected systematically in a format that enables comparisons across studies of a similar nature. An aspiration would be to be able to search across all granted licences of a similar genre (e.g. for descriptions of harms, refinements and actual severity etc.), and to link the predicted severity in each project licence with the actual severity subsequently reported.

Recommended Action 2 [2]:

The estimation of harms likely to be experienced by individual animals should be realistic and incorporate all known sources of harm. There is scope for ASRU to provide more guidance to applicants to ensure that harms are described realistically: i.e., they should consider the animals' likely experiences, in terms of potential pain, suffering distress or lasting harm (not just during procedures but over their lifetime), rather than merely detailing the practical steps involved in a procedure (e.g. 'blood will be taken'). This process would be facilitated by ensuring that future developments in the electronic licensing system enable better documentation of 'lifetime experience'.

Recommended Action 3 [3]:

ASRU should consider expanding the scope of the thematic inspections it already undertakes. In particular, to consider whether the outcomes of these inspections could be shared with all relevant stakeholders (with their permission for disclosure).

2. Assessing Cumulative Suffering

Recommended Action 4 [5 - 8]:

ASRU should:

- Define clearly the concept of lifetime experience in terms of what can and should be considered and assessed by the regulator within the HBA process.

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[1] numbers in parenthesis [..] refer to the recommendation, which is described in full in the HBA review.

- Keep up to date with latest findings and thinking in the fields of cumulative suffering, including selection and implementation of relevant tools and approaches for recognising and recording cumulative severity.
- Strive to ensure that claims relevant to the HBA are impartial and scrutinised in the light of scientific evidence, particularly in respect of habituation / sensitisation.

3. Strategies to Minimise Suffering

Recommended Action 5:

ASRU to consider the ASC's view that there is a foreseeable risk of a conflict between societal values and the scientific justification for animal use, arising from (1) the requirement in A(SP)A to use animals with the lowest capacity to experience pain, suffering, distress or lasting harm (Schedule 2C (18b)); and (2) the requirement in A(SP)A to use specially protected species (cats, dogs, equidae or non-human primates) only when the use of another species is not considered to be possible (Schedule 2B (4)). When using certain protocols, this conflict could lead to a mouse or rat experiencing more suffering than a dog, for instance.

Recommended Action 6:

If the scenario described in Recommendation 5 occurs, the ASC asks ASRU to:

- Refer any such cases to the ASC
- To document the criteria applied when granting special protection
- To ensure that the matter is taken into account in any future policy development

Recommended Action 7 [9]:

ASRU to:

- Ensure that researchers always provide a robust rationale for the scientific need and the ethical justification for using a 'severe' model or procedure.
- Encourage thorough scrutiny and constructive challenge of the rationale, by all involved in developing and/or reviewing project licence applications, prior to submission.

Recommended Action 8 [10]:

Projects that could cause severe suffering should continue to be given intense scrutiny at every stage of their design, including the ethical review process. When severe suffering is deemed to be unavoidable, this scrutiny should give particular consideration to the likelihood of achieving the objectives of the study as well as the harm(s) versus benefit(s). Granting of a licence should be considered only when there is an exceptionally high level of expected benefit and likelihood of success. The work should be monitored further, in respect of the reporting and publishing of the findings.

Recommended Action 9 [11]:

ASRU to encourage effective feedback and dissemination of information by researchers, AWERBs and others involved in HBA, on successful refinements and ongoing concerns, both as the projects progress and at their conclusion (see: Fig 1).

Recommended Action 10 [12]:

ASRU to continue to ensure that everyone involved in HBA understands that assessment of harm, including decisions on humane end-points, is not undertaken using the severity categories alone, but that all adverse effects are taken into account, particularly when approaching the upper limit of any severity classification.

Recommended Action 11 [13]:

ASRU to encourage each establishment to design its own strategy for eliminating severe suffering.

4. Enhancing the Evaluation and Realisation of Benefits

Recommended Action 12 [8, 14 & 17]:

ASRU to ensure that:

- The rigour and legitimacy of the HBA is supported by the use of existing research tools [8 & 17]
- Research objectives and project milestones for realising research benefits are realistic, transparent and accountable [14]
- Failure to achieve a milestone is given due consideration in respect of how this affects the HBA
- There is timely (e.g. within 3 months of a project being licenced, or of retrospective assessment being carried out) publication into the public domain of non-technical summaries and updated NTSs (when applicable).

Recommended Action 13 [15]:

ASRU to ensure that journal impact factors for a researcher's (or research group's) past publications are not given undue emphasis when considering quality of science and likelihood of a project's success.

Recommended Action 14 [16]:

ASRU should encourage researchers and establishments to exploit opportunities to enhance emerging benefits, *over the lifetime of project licences,* with particular reference to systematic review and meta-analysis.

Recommended Action 15 [19 & pg 56]:

ASRU to consider:

- How it currently considers the issues raised in the checklist in Box 1
- Transparency in respect of appraisal of a licence for compliance with the points listed in Box 1,

- How to ensure that PPL applications are not approved without compliance with all points listed in Box 1
- The CPD it provides to inspectors in respect of experimental design, and the reporting (and archiving) of data etc.

Recommended Action 16 [23]:

ASRU should explore the scope for enabling more nuanced HBA of products tested under generic toxicology licences.

ASRU to provide advice to establishments involved in regulatory toxicology testing to ensure that their local mechanisms for weighing harms and benefits consider the context of the types and utility of the specific substances / products being tested, the opportunities for data-sharing, and the contribution to ongoing HBA review in this field.

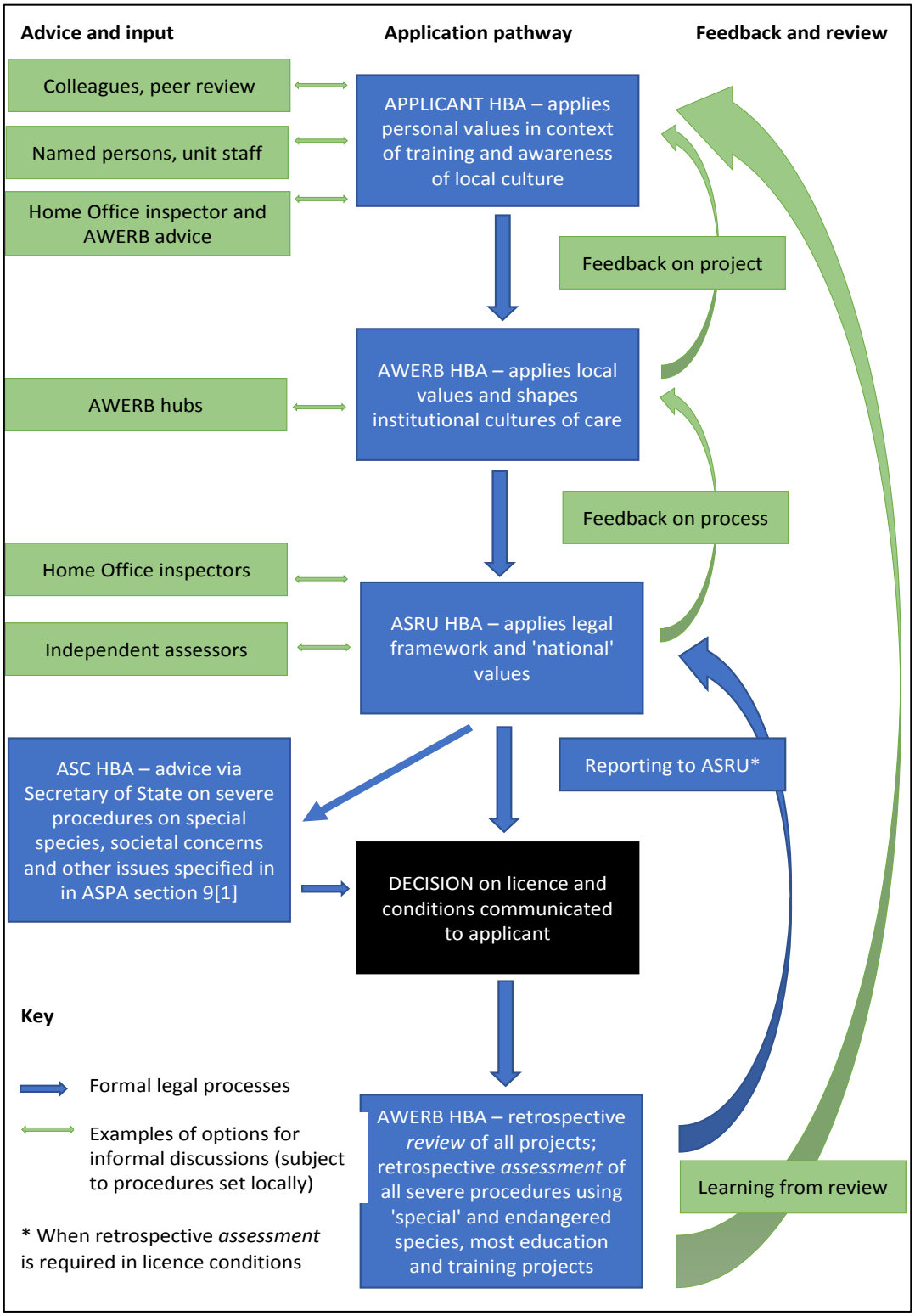
5. Incorporating Societal Concerns

Recommended Action 17 [24]:

ASRU to:

- Be transparent, particularly in respect of the criteria it uses for highlighting ethical, novel or contentious issues that are relevant to HBA
- Consider how it informs itself of societal concerns and their evolution
- Proactively horizon-scan for issues that may raise particular societal concerns
- Include Fig 1 (page 16 of HBA review) in future guidance

Figure 1: Harm–benefit analysis, advice, and feedback processes for project licence applications



BOX 1

- Has the review of prior work included a systematic review of past animal studies?
- Has the researcher employed the Experimental Design Assistant, or other tools, to calculate and demonstrate appropriate statistical power?
- Are methods of randomisation and blinding (masking information about a test from participants until outcome(s) are known) adequate for removing bias?
- Are researchers aware of and compliant with *Animal Research: reporting of In Vivo Experiments* (ARRIVE) guidelines in their past and planned publications?
- Is the research clear about how it is oriented on the basic/applied spectrum and amenable to review if research changes? Are the intended benefits from oriented basic research appropriately explained?
- Do researchers demonstrate the potential to interact effectively and responsively with others engaged in translational research (for example, clinical contexts, policy communities, learned societies, and commercial outlets)?
- Is regulatory research clear and transparent about the specific direct benefits (for example, marketing and licensing)? Are licensing requirements mandatory or are there flexible and alternative routes for development of the work?
- Do all researchers indicate how new opportunities to recognise and disseminate benefits can be identified and enhanced during and after the research?
- Do research programmes identify the potential to deliver wider benefits (for example, sharing good practices in the 3Rs, new data sharing opportunities)?
- Are proposals for gathering, archiving, and providing access to research data adequate and appropriate?
- Do publication plans include the intention to publish all valid results from the study?
- Does animal research that involves known or likely societal concerns include the opportunity to engage broader social perspectives in and through this work?