ANNEX A

Home Office response to the ASC's recommendations on the ASRU Harm-Benefit Analysis

1. Assessing Harms Experienced By Animals

Recommendation Action 1 [from Report Recommendation 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.

The Home Office accept this recommendation. The Home Office agree that overview and comparison of both prospective and actual severity informs better understanding of severity and the delivery of the 3Rs (Replacement, Reduction and Replacement). To collect such data, and make useful comparisons, requires a system that integrates the end to end licence process. The Animals in Science Regulation Unit (ASRU) has been building a replacement I.T. system (ASPeL) that was rolled out in August 2019 and is built with new and improved functionalities. The new system seeks to address this recommendation. Severity and expected adverse effects data will be collected systematically in the protocols. Search capabilities will be enhanced within the project licence system, which will enable ASRU to have read across of similar studies to inform 3Rs delivery. ASRU will continue to update the ASC on delivery of this outcome.

Recommended Action2 [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'.

The Home Office accept this recommendation. The Home Office agree that expected sources of harm need to be described in project licence applications

with sufficient detail and the right information to inform the Harm Benefit Analysis. The project application process for the replacement I.T. system is structurally different to the previous process and incorporates guidance notes to applicants which set the information required on expected harms to animals. The guidance notes are an enhancement of published advice currently included in ASRU's Annotated Project Licence form. They have also taken account of the stakeholder feedback that was collected in preparation for the I.T. system development. ASRU will monitor the quality of applicant responses to these questions once the system has been launched and will review the structure of the application form over time. Questions will be amended after a structured review of the new application form if the questions are not achieving the outcomes that we are seeking in this area.

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).

The Home Office accept this recommendation. The Home Office agree that thematic inspections have already been valuable as part of animals in science regulation as a tool to gather data and focus on specific issues. The Home Office agree that the outcomes and impact of the inspection programme should be communicated appropriately to all relevant stakeholders. The outputs of these activities are already published on an annual basis in our Annual Reports (https://www.gov.uk/guidance/research-and-testing-using-animals#annual-reports). Further, the results of thematic inspections, and the inspection programme overall, are regularly presented by ASRU officials at National and International level. The progress of the recent thematic inspections into mouse handling, re-use of single use needles and failures to provide food and water have been presented at conferences this year: the Laboratory Animal Science Association (LASA) and the Institute of Animal Technology (IAT). ASRU have also discussed the thematic inspections at stakeholder meetings with protection groups, welfare groups and Bioscience groups. The Home Office are making plans to expand the programme to drive the implementation of the 3Rs, improve animal welfare, and inform improved culture of compliance and care in establishments. The Home Office will continue to identify stakeholder engagement opportunities to maximise the benefit of the inspection programme.

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.**
- **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.**

The Home Office accept this recommendation. The Home Office agree that the scope of what should and can be considered during the assessment of harm needs to be defined. The Home Office will clarify the information required for and considered in the Harm Benefit Analysis in the new ASPeL system. Applicants are encouraged to present clear information about harms which will inform the harm-benefit analysis. This incorporates the evolving concepts of lifetime experience and cumulative severity. There are a number of documents available to applicants and ASRU that support delivery of high quality Harm Benefit Analysis in the development, assessment and delivery of project licences: the EU Working Group document Project Evaluation and Retrospective Assessment; the EU Working Group document on Severity Assessment Framework; ASRU's Guidance (Appendix I); and, ASRU's Harm Benefit Analysis Advice Note. The latter document sets out in detail how cumulative severity and lifetime experience is already monitored/included in the Harm Benefit Analysis. The Home Office agree that as more evidence emerges the scope of what should be considered during assessment of harm should be reviewed and refined. The Home Office will deliver these outcomes through ASPeL as the system continues to be developed.

It is important that ASRU's officials can ensure that applicants and project licence holders keep up to date with the latest findings on cumulative suffering, including selection and implementation of relevant tools and approaches for recognising and recording cumulative severity. To support this, ASRU Inspectors attend numerous conferences each year where the latest evidence is presented on assessment of laboratory animal welfare and suffering and we will take advantage of specific opportunities to focus on these concepts during attendance of scientific meetings. Emerging thinking on the concepts of cumulative suffering will continue to be included in both the

Inspectorate professional development programmes and referenced in the training programme for new Inspectors.

We would welcome ongoing critical dialogue with the ASC about these concepts to determine how they can be further embedded in our processes.

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.

The Home Office accept this recommendation. The Home Office suggest that such potential conflicts should be identified but are likely to be unusual occurrences. The law, as written and applied, considers societal values. This means that intense scrutiny is applied to the use of specially protected species such as dogs and primates because the public are particularly concerned about their use. ASRU will work with the ASC to further understand these risks and would welcome examples from the ASC of such conflicts and how they could be managed.

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**

The Home Office accept this recommendation. The Home Office will refer relevant cases to the ASC and will consult the ASC for advice as required.

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.**

The Home Office accept this recommendation. All project licence applications are given thorough scrutiny by ASRU Inspectors during the Harm Benefit Analysis process. ASRU delivers a proportionate project application assessment process. Greater scrutiny is given to applications that include severe procedures. Robust justification is required for all projects submitted to ASRU. ASRU asks for specific justification for the need for a severe model or procedure during the application process and has published guidance in its annotated project licence form to clarify the information required to justify such procedures. Full details on the Harm Benefit Analysis process are contained with the documents at Recommended Action 4 above.

This recommendation is being addressed by delivery through the new ASPeL system, which will facilitate applicants in sharing their draft applications with others within their establishment for collaboration and review prior to submission. This capability was not in ASRU's previous licensing system.

ASRU take into account the occurrence of severe procedures when planning inspection activities, thus focusing Inspectorate time on work that involves higher levels of animal suffering. The Home Office recognise that a more outcome-focused approach could impact significantly on reduction of severe procedures if more refined methods are available to achieve the scientific objectives. Thus, work of particular concern will be considered when planning the themed and outcome-based inspection programme to evaluate whether this could impact on reduction of severe suffering.

An important part of the UK licence process is the Animal Welfare and Ethical Review Body (AWERB). These bodies are required at every UK establishment. The role of the AWERB includes reviewing project licence applications and therefore considering the rationale for scientific need and ethical justification – not only for severe models. It is entirely within the AWERBs remit to scrutinise and challenge the rationale in the development of the application prior to submission. ASRU will continue to monitor the effectiveness of AWERB function in delivering this role.

As well as guidance on AWERB function published by the Home Office, LASA has published guiding principles on AWERB function at: http://lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf

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.

The Home Office accept this recommendation. AWERBs are required to advise on the application of the 3Rs. The AWERB should also advise the establishment licence holder whether to support project licence application proposals and provide a forum for discussion for ethical advice. The scrutiny of severe procedures is an important part of the AWERB's role. ASRU will continue to focus activity on AWERB function in this during inspection activities and advise when this function is not compliant with requirements under ASPA.

The mandatory requirement for Harm Benefit Analysis requires that all harms to animals are justified by the likely benefits to be accrued. Projects that have procedures classified as severe must also undergo a retrospective assessment. This provides further opportunity to monitor the outcomes of projects that contain severe procedures and will inform future decision making. The Home Office recognise that in the future retrospective assessment will be an important tool to drive 3Rs delivery and ASRU will use the information gathered to better inform 3Rs outcomes.

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).

The Home Office accept this recommendation. A key role of the ASRU Inspectorate is to encourage the dissemination of refinement. ASRU shares information between Inspectors and within the scientific community, nationally and internationally, with mutual agreement from all parties and ensuring

personal, commercially and intellectually sensitive information is protected. The mechanisms we use include: ASRU Annual Report; internal communications; published newsletters; presentations at various fora; stakeholder meetings; Establishment meetings and Annual Risk Meetings; and inspection visits.

There are several mechanisms that the Home Office will use to deliver the proposed outcomes in this recommendation. In May 2018 ASRU and the NC3Rs signed a Memorandum of Understanding (MoU) which will provide a framework to work more closely on shared 3Rs concerns. This will facilitate effective dissemination of successful refinements on ongoing concerns by ASRU. ASRU continue to develop an outcome-based approach to the inspection programme which will also focus on ongoing concerns which need to be addressed. Outcomes from inspection activities that impact on the 3Rs will be described in its Annual Report.

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.

The Home Office accept this recommendation. The assessment of harm must take into account the expected harms that are likely to occur during the authorised work, rather than using severity categories alone. The Home Office recognises that this issue sometimes leads to misunderstanding of what is actually considered in the Harm Benefit Analysis process. To clarify how the process is undertaken, The Home Office has published detailed guidance in this regard, e.g. HBA Advice Note and the Annotated Project Licence Application form, which sets out the information needed for the Harm Benefit Analysis. The replacement ASPeL system addresses this recommendation by incorporating guidance notes into the system to clarify the level of detail needed. This guidance clarifies that harms are not assessed using severity categories alone. ASRU are now developing a standards base approach to project licence assessment which will continue to refine how assessment is undertaken.

Recommended Action 11 [13]:

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

The Home Office accept this recommendation and agree that that this is a desirable outcome for the future. ASRU agrees that severe procedures should

continue to be assessed with a high level of scrutiny and will encourage establishments to build strategies to minimise suffering while delivering their scientific objectives. Currently there are some scientific situations where severe suffering is still needed to achieve important scientific objectives. Therefore, the category “severe” is still needed for some procedures authorised under ASPA. The regulatory system ensures that animal research and testing is carried out under controls which keep suffering to the minimum.

4. Enhancing the Evaluation and Realisation of Benefits

Recommended Action 12 [8, 4 & 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).**

The Home Office accept this recommendation. As new research tools are developed for recognising and recording cumulative severity, those involved in evaluating suffering should consider their use where they add value. Before deciding that animals are used, the current evidence base must be reviewed thoroughly by applicants. This may include systematic review and meta-analysis of published literature. Under ASPA, animals can only be used where the scientific objectives could not be achieved without their use.

Researchers and AWERBs should review the milestones in extant projects to continuously monitor the value of the animal use. ASRU inspectors assess delivery of projects and compliance action is taken if breaches of the licence conditions relating have taken place. Standard Condition 18 reporting has been introduced to notify ASRU if constraints on severity or observance of other controls described in the project licence have been or are likely to be breached, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/705833/Standard_Condition_18_Advice_Note.pdf.

This tool provides checks and balances for the establishment to assure itself, and ASRU, of delivery of the Harm Benefit Analysis as agreed in the granted licence.

The Harm Benefit Analysis should be a continuous process throughout a project, and the emerging benefits in relation to the actual harms should be regularly reviewed by researchers and AWERBs. Retrospective assessment is now a requirement under ASPA for some projects and this is a further opportunity to reflect on whether the expected benefits have been delivered as a result of harms.

The replacement ASPeL system has been designed to facilitate more timely publication of NTSs and we are working towards a target of 3 months of publication. A future aspiration is to develop a database which will allow easy searching of the data contained within them.

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.

The Home Office accept this recommendation. When assessing new applications, inspectors consider previous projects by the applicant and what benefits were achieved, including any animal work related refinements and focus on the 3Rs. During Harm Benefit Analysis Inspectors consider criteria such as the applicant's track record with regards to publications and animal use, to determine how likely the benefits are to be delivered. Journal impact factors should not be given undue emphasis during assessment. Inspectors will take this into account during project evaluation. Each project is reviewed on a case-by-case basis, both in terms of science quality and likely delivery of benefit. ASRU will consider updating their guidance on how such criteria are considered during Harm Benefit Analysis and would value further dialogue with the ASC on this issue.

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.

The Home Office accept this recommendation. There is a legal requirement for 3Rs delivery and benefits from animal use should be maximised. The use of systematic reviews is now referenced in our published notes for applicants. To

address this recommendation, these notes will be further referenced and embedded in the new ASPeL system.

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.**

The Home Office accept this recommendation. The matters raised in Box 1 are addressed during the project licence application process and are raised in ASRU's published advice for applicants, or elsewhere provided by inspectors. They may also be considered at establishment level, for example as part of the AWERB's responsibilities. ASRU agree that inspectors should continue to be aware of these requirements and this is reflected in their training. Inspectors have a diverse range of expertise and experience and many hold PhDs and/or have research experience. Experimental design is therefore part of the knowledge base of the Inspectorate. However, the relevant expertise should be on how to develop good experimental design, within the project licence, not on the experimental design of any given project. ASRU must be assured that the applicant has suitably constructed the project so as to best gather data appropriate to the objectives sought. Licensed establishments have a wide range of resources in statistical expertise and experimental design. To support this process Inspectors ask for information regarding the available resources and direct applicants towards specific tools, such as the NC3Rs' experimental design assistant. This is part of the training for new Inspectors and we will be embedding specific guidance notes for applicants into the new ASPeL system. The success of the guidance and questions for applicants will be monitored as the new system is rolled out.

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.

The Home Office accept this recommendation. ASRU work with many other national and international regulatory authorities who have the responsibility for licensing effective and safe products. These authorities decide what data are required from *in vitro* and *in vivo* tests in order to make sound scientific judgements as to the safety and efficacy of these products to the end user and at all stages of development and manufacture.

As part of the delivery of the new e-licensing system, work is underway to review how these types of licence application are prepared and assessed. This will specifically address the points made in this recommendation. ASRU cannot vary the tests required by other regulators, but we do consider the overall level of knowledge and governance in the establishment as part of our Harm Benefit Analysis process. Under the new ASPEL system standard conditions will automatically be added to the licences requiring that the ASRU Inspector must be contacted by the applicant if a lower impact test is available but rejected by a regulator in favour of animal studies.

This enables a specific Harm Benefit Analysis to be carried out on the specific test and only if there is suitable scientific justification for animal studies will prospective authority be granted.

ASRU has a Memorandum of Understanding with the NC3Rs and signposts applicants to the NC3Rs website which contains links to all publications from the NC3Rs Toxicology and Regulatory sciences programme which is involved in refining regulatory tests and working with other regulators to gain their acceptance.

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.**

The Home Office accept this recommendation. Pro-active horizon scanning of matters that raise societal concern is an important part of ASRU's work. The ASRU policy team have broad oversight of how animals in science is portrayed in the media. They deal with all external correspondence to the Home Office in this policy area, which includes letters from the public, animal rights pressure groups and Members of Parliament on behalf of their constituents. ASRU is engaged with other Government Departments to appreciate the different perspectives across Government. Senior ASRU staff meet with diverse stakeholder groups three times a year to discuss a wide range of issues that are primarily driven by the stakeholders' interests. The groups include all major stakeholders across the spectrum of protection and welfare groups. ASRU is engaged with BEIS and the public attitudes survey conducted annually by Ipsos Mori and we have links to the Science Media Centre. ASRU Inspectors and the ASRU policy team monitor media and public content as a matter of course.

These mechanisms provide ASRU with a nuanced understanding of how the public view this policy area. In the future, ASRU would welcome further advice from the ASC regarding how other methods could be used to gather such information.