

## APPENDIX 1

### Report of results of a LASA/APC Questionnaire for PPL holders on retrospective reporting of the actual severity of animal procedures

#### 1. Questionnaires returned

Questionnaires (blank copy attached at end of this report) were distributed to all active project licence (PPL) holders in nine designated establishments: three large universities, three research institutes, and three industry establishments.

A total of 168 completed questionnaires were returned, representing 171 project licences - approximately 6% of those in force<sup>1</sup>. 104 were from universities, 32 from research institutes, and 35 from industry establishments. The overall response rate was 37%. See Table 1 below for further details.

**Table 1: Questionnaires returned, by establishment type**

Establishment	N active PPL holders	N responses from PPL holders	Response rate (%)
University A	125	37	30
University B	106	13	12
University C	120 <sup>i</sup>	54	45
<b>Universities total</b>	<b>351</b>	<b>104</b>	<b>30</b>
Government research agency	15	12	80
Research Institute 1	25	12	48
Research Institute 2	14	8	57
<b>Research Institutes total</b>	<b>54</b>	<b>32</b>	<b>59</b>
Pharmaceutical company I	28	16	57
Pharmaceutical company II	15	11	73
CRO	12	8 <sup>ii</sup>	67
<b>Industry total</b>	<b>55</b>	<b>35<sup>iii</sup></b>	<b>64</b>
<b>GRAND TOTAL</b>	<b>460</b>	<b>171<sup>iv</sup></b>	<b>37</b>

*i Includes several large institutes and three (former) teaching hospitals*

*ii 5 project licence holders, between them holding 8 licences, returned completed questionnaires*

*iii 32 completed questionnaires – for reason given in ii*

*iv 168 completed questionnaires – as per ii*

#### 2. Current practice in recording actual severity of adverse effects

43% (N = 72) of respondents say that they "always" record the adverse effects actually experienced by the animals in the protocols they use. 36% (N = 61) say that they "sometimes" do this; and 21% (N = 35) that they "never" make such records. These figures are broken down by type of establishment in Table 2 overleaf.

<sup>1</sup> Based on 2003 Statistics (latest available).

**Table 2: Overall percentage respondents currently recording actual severity**

**Q1** Ignoring any instances in which the severity limit is breached, do you currently record the adverse effects actually experienced by the animals in the protocols you use?

<b>Establishment type</b>	<b>"Always"</b> %	<b>"Sometimes"</b> %	<b>"Never"</b> %
University	33	41	26
Research Institute	44	37	19
Industry	75	19	6
<b>OVERALL (N=168)</b>	<b>43</b>	<b>36</b>	<b>21</b>

Care should be taken in drawing conclusions about current practice from data in the "sometimes" and "never" categories above. Answers to more detailed questions show that recording practice is influenced by the protocol severity limit and adverse effects actually experienced by the animals, as well as, in some cases, the purpose of the work. These are considered in turn below.

### 2.1 Variation in recording practice by protocol severity limit

Table 3 (overleaf) shows, in general terms, how recording practice varies with protocol severity limit (also divided by establishment).

It should be noted that 51% (N= 18) of the licences in which adverse effects are "never" recorded (Total N = 35) include only mild and/or unclassified protocols. Table 4 illustrates this point, by presenting data on the maximum severity of protocols in the licences of PPLs who report that they "never" record actual adverse effects.

Some of those who report that they "never" record actual adverse effects in moderate or substantial protocols point out that, in practice, their protocol(s) cause significant adverse effects only very rarely (a moderate limit being regarded as a "safety net") or that the adverse effects of the protocols are very consistent/standardised.

**Table 4: Maximum severity of protocols in licences of PPLs who report that they "never" record actual adverse effects**

<b>Maximum protocol severity limit within licence</b>	<b>% of licences for which severity is "never" recorded:</b>			
	University	Research Institute	Industry	<b>TOTAL (%)</b>
	N = 27	N = 6	N = 2	N = 35
Unclassified	4	0	0	3
Mild	44	67	100	51
Moderate	41	33	0	37
Substantial	11	0	0	9

In addition, record keeping of actual adverse effects varies *within* 9 out of 61 licences in the "sometimes" category (15%). These licences include unclassified and/or mild protocols, for which adverse effects are "never" (or only "sometimes") recorded together with moderate and/or substantial protocols, for which adverse effects are "always" recorded

Further details of the circumstances in which project licence holders report that they 'sometimes' record actual severity are presented in Table 5 on page 4.

**Table 3: Variation in records currently made of actual severity, by protocol severity limit**

**Q2** For which kinds of protocol do you record these actual adverse effects? and  
**Q5** Please indicate the severity of the protocol(s) included in your project licence(s)

	Protocol severity limit		
<b>Universities:</b>			
N respondents to Q2 whose licences include protocol(s) of severity:	<b>Mild</b> N = 70	<b>Moderate</b> N = 73	<b>Substantial</b> N = 9
% of these respondents recording actual severity for those protocols:			
<b>Always</b>	36%	40%	44%
<b>Sometimes</b>	34%	42%	22%
<b>Never</b>	30%	18%	33%
<b>Research Institutes:</b>			
N respondents to Q2 whose licences include protocol(s) of severity:	<b>Mild</b> N = 23	<b>Moderate</b> N = 24	<b>Substantial</b> N = 11
% of these respondents recording actual severity for those protocols:			
<b>Always</b>	43%	54%	91%
<b>Sometimes</b>	39%	38%	9%
<b>Never</b>	17%	8%	0
<b>Industry establishments:</b>			
N respondents to Q2 whose licences include protocol(s) of severity:	<b>Mild</b> N = 20	<b>Moderate</b> N = 22	<b>Substantial</b> N = 5
% of these respondents recording actual severity for those protocols:			
<b>Always</b>	80%	73%	100%
<b>Sometimes</b>	15%	27%	0
<b>Never</b>	5%	0	0
<b>OVERALL:</b>			
N respondents to Q2 whose licences include protocol(s) of severity:	<b>Mild</b> N = 113	<b>Moderate</b> N = 119	<b>Substantial</b> N = 25
% of these respondents recording actual severity for those protocols:			
<b>Always</b>	45%	49%	76%
<b>Sometimes</b>	32%	39%	12%
<b>Never</b>	23%	13%	12%

**Table 5: Circumstances in which actual severity is ‘sometimes’ recorded**

<b>Q3</b> <i>When do you record these actual adverse effects? (Please mark all that apply)</i>	% respondents who record severity ‘sometimes’ N = 61
When the adverse effects look likely to approach the severity limit	26
When the adverse effects are uncertain or difficult to predict	33
When a protocol causes unanticipated or unusual adverse effects in practice	70
When a protocol involves novel techniques, or techniques that are new to the project team or the establishment	43
Other*	8

\* Examples given:

- *When the adverse effects are part of the desired effect of the procedure (e.g. cyanosis as an indicator of heart failure) / When the experimental aim is to monitor adverse effects of an intervention (e.g. monitoring disease severity in infection and immunology studies) / Or when adverse effects otherwise impact on the experimental result (4)*
- *When possible adverse effects manifest themselves, since this would not be usual (1)*
- *Characterising phenotype in new mutant/transgenic animals (2)*
- *Aim to cover all animals in moderate protocols, but cannot do this fully because of demands of recording GM animals (1)*

## 2.2. Variation in recording practice by type/purpose of work

As the answers under ‘other’ in Table 5 indicate, there are vital experimental, as well as animal welfare, reasons for recording adverse effects in many cases. This may, in part, explain the overall differences in recording practice between the different types of establishment as shown in Table 2. For example, many of the industry and one of the research institute replies refer to work in which the aim is to record the effects of novel treatments/therapies – hence recording of *all* adverse effects (as well as ‘no’ effects and ‘beneficial’ effects) is an essential part of the experimental approach. Similarly, where novel GA animals are produced (as done on a wide scale in two of the RIs), there is a need to characterise the phenotypic effects of the genetic change, and so all adverse (as well as other) effects are always recorded initially.

Responses to the questionnaire provide qualitative evidence of such differences in recording practice according to field of work, but unfortunately the answers do not lend themselves to quantitative analysis.

## 2.3 Ease of Returning to the Home Office information currently recorded, by severity category

As shown in Table 2, 79% (N = 133) of respondents report that they ‘always’ or ‘sometimes’ record the adverse effects actually experienced by the animals in the protocols they use.

Of these, 39% (N = 52) say that they record the information in a way that would allow them easily Return to the Home Office the number of animals used in each protocol by category of severity of adverse effects actually experienced (i.e. mild, moderate or substantial).

57% (N = 76) say that they do not record the information in a way that would allow an easy Return by category of severity; and 4% (N = 5) are uncertain.

These figures on ‘ease of Return’ are broken down by type of establishment in Table 6a overleaf.

**Table 6a: Ease of Return of information currently recorded**

**Q4** *If you always or sometimes record the adverse effects actually experienced by the animals in the protocols you use, then: Do you record the information in a way that would allow you easily to Return to the Home Office the number of animals used in each protocol by category of severity of adverse effects they actually experienced (i.e. mild, moderate or substantial)?*

<b>Establishment type</b>	<b>'Yes'</b> %	<b>'No'</b> %	<b>'Not sure/perhaps'</b> %
University	42	53	5
Research Institute	50	46	4
Industry	23	77	0
<b>OVERALL (%) (N=133)</b>	39	57	4

Comments on the difficulties in making such a Return are summarised in Table 6b below. These relate mainly to the extra *burden* (administrative bureaucracy, time, or other resources) that this would present, particularly because the information is not necessarily recorded in a *format* that would allow easy extraction of data that could enable the severity to be categorised. Some industry PPL holders also note that the information might be held in a number of different *locations*, recorded by different people for different purposes. Respondents also point to a number of areas of uncertainty, such as dealing with protocols involving breeding GA mice, and categorising adverse effects not directly connected to the protocol, including unexpected deaths of animals, or deaths due to ageing.

**Table 6b: Comments re. ease of Return of adverse effect information currently recorded**

<b>Difficulties in Returning information currently recorded by severity category</b>	<b>Establishment type</b>		
	University N = 15	Research Institute N = 8	Industry N* = 16
<b>Burden:</b> administrative bureaucracy, time, other resources	6	2	2
<b>Format:</b> difficulties determining/extracting severity category from current records	2	2	10
<b>Location:</b> information held in a variety of locations, recorded by several different people	0	0	3
<b>Difficulties dealing with unexpected effects not directly connected to protocol:</b> Including dealing with unexpected deaths or deaths due to ageing, also 'desirable' cf. 'undesirable' effects	3	0	1
<b>Difficulties in reporting for GA animals, including:</b> Tracking and recording animals which are moved from breeding to other protocols; and particular difficulty when GA animals with 'normal' phenotypes are moved to protocols which are mild for wild-type animals, but which 'must' be recorded as moderate due to the origin of the GA animals	1	3	0
Difficulty of enforcing the requirement to Return information	0	0	1
Managing the process	2	0	0
Subjectivity of categorisation process	1	0	1
Events recorded only when uncertain, repeatedly observed or close to the severity limit	0	1	0

\* Two respondents made comments in two categories

Similar difficulties are raised in the more extensive comments recorded in Table 7b on page 7, which are related to the ease of *recording* information on actual adverse effects *by severity category*, and are discussed below.

### 3. Method of recording severity of adverse effects

The questionnaire asked respondents:

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**Q7** *How would/do you record the severity of adverse effects (mild, moderate or substantial) actually experienced by the animals in your protocols?*

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Respondents report that they (would) record the actual effects on the animals either in hand-written form or in computer databases (which in some cases are Company/establishment-wide systems).

A number of different people make (or could make) the records: the PPL holder, the PIL(s) working under the PPL, Study Directors (in industry), the Named Veterinary Surgeon (particularly with regard to more general health monitoring) and animal technicians. In some cases there would be a need to co-ordinate/retrieve data from a number of different sources in order to make a Return, e.g. breeding records, PIL records, laboratory day/log books, experimental results themselves.

20 respondents mention the use of 'welfare scores', 'scoring sheets' or other grading schemes to help in *categorising* severity (e.g. the FELASA scheme), 3 of whom seem to be referring to schemes for characterising phenotype in GA animals. 3 say that there would be variation in categorisation even with use of such schemes, and one that they have tested clinical score systems but found them to be "neither simple nor reliable" – preferring to use weight loss as the indicator (infection and immunology studies). N.B. Because this was a very open question, lack of mention of use of a scoring scheme does not imply that one is not/would not be used.

None of the respondents say that they specifically and routinely record severity *by category* – though the use of clinical scoring schemes for implementation of humane end-points could result in such records, and one respondent says that the category would be recorded "if the study had to change course because the severity band [limit?] had been/was in danger of being exceeded". A number of respondents specifically say that they do not currently record by severity category and that this would have to be added into their recording system.

One (industry) respondent asserts that "Some form of exception reporting would have to be the norm", and another (RI) makes a similar point in relation to monitoring GA mice, saying that they would record severity:

When/if something falls outside an agreed framework. Currently almost all of my work entails dealing with animals that are indistinguishable from wild-type. If they are different in any way we would be very keen to publish the fact.

#### 3.1 Difficulties in recording actual severity of adverse effects (mild, moderate or substantial)

As a follow-up to Question 7, respondents were also asked whether they foresee any difficulties in recording the severity of adverse effects by the method they described.

Overall, a little more than a third of respondents (35%, N = 59) believe that there are, or would be, difficulties in recording severity of adverse effects by category (mild, moderate, substantial).

62% (N = 104) say that there are/would be no particular difficulties (though four of these actually say "No, but..." and comment on bureaucratic implications).

2% (N = 6) say that the difficulties depend on the nature of the protocol involved.

Table 7a overleaf breaks these figures down by type of establishment. The types of difficulty that respondents mention are recorded in Table 7b, also overleaf.

**Table 7a: Difficulties foreseen in recording adverse effects by severity category**

<b>Q7 How would/do you record the severity of adverse effects (mild, moderate or substantial) actually experienced by the animals in your protocols? Do you foresee any particular difficulties in doing this?</b>			
<b>Establishment type</b>	<b>'Yes' %</b>	<b>'No' %</b>	<b>'Yes or No' %**</b>
University	26	72	2
Research Institute	50	42	6
Industry	50	50	0
<b>OVERALL (N=167)</b>	<b>35</b>	<b>62</b>	<b>2</b>

\* Depending on protocol

**Table 7b: Comments on difficulties in recording adverse effects by severity category**

<b>Difficulties in recording adverse effects by severity category</b>	<b>Establishment type</b>		
	<b>University N = 30</b>	<b>Research Institute N = 21</b>	<b>Industry N = 16</b>
<b>Burden:</b> administrative bureaucracy, time, other resources	13	11	6
<b>Subjectivity:</b> difficulties in classifying severity, interpreting signs; variations between licensees (and others)	9	4	9
<b>Difficulties in dealing with very mild procedures which apparently have no adverse effect:</b> 3 mentioned taking a feather from a wild bird; other respondent holds a 'biological service' licence	4	0	0
<b>Difficulties in dealing with GA mice:</b> 2 commented on bureaucratic implications if a phenotype analysis was required on every mouse born under every protocol; 2 said that for most/all animals records would be 'no effect'	1	3	0
Possibility of errors that could compromise validity of information	0	2	0
FOI implications of putting the information in public domain	0	1	0
Recording may be particularly complex in toxicity studies	0	0	1
Additional complexity in HO Returns form	1	0	0
<b>Other:</b> Main adverse effect is secondary infection (?) Difficulty of recording from 1000s of zebra fish	2	0	0

### 3.2 Further comments on difficulties

#### **Burden**

As in comments on 'ease of Return' of information that is currently reported (Table 6b, page 5), respondents' views on difficulties in recording and reporting the severity of actual adverse effects focused on the extra burdens that this would bring and, in some cases, on how this would detract from more pressing duties to science and animal welfare – e.g. this comment from a respondent in industry:

Just another bit of bureaucracy that will burden the licensee and detract from duties more closely associated with animal care and welfare

and also this particularly strong comment:

We are already spending most of our days gathering data which will probably sit in some official's tray. This is a prime example of a small but significant additional workload which will detract from our ability to actually get on with science. The information is in our publications. The legislators wish that "serious effort should be made to provide better statistics on animal suffering". Officials can make the 'effort' to read our papers if they wish. These incremental requests for documentation are effectively a way of achieving a ban on animal experimentation without a mandate from the public or parliament. The universities should unite in resisting additional requests for statistics, not devise ways of complying.

#### **Subjectivity**

Comments on difficulties of interpreting clinical signs and categorising severity include several questions and ideas, and raise a number of general issues, including:

- What is meant by an 'intermittent' cf. a 'transient' effect?
- Is surgery with good analgesia 'mild' or 'moderate'?
- We have a classification system for severity of toxicological adverse effects, but no similar classification of adverse effects resulting from e.g. surgery, restraint, dosing, sampling etc.
- How to deal with zebra fish – "less is known about pain thresholds in this (cf. other) species"
- If each animal on a long-term experiment had a very transient moderate response, but for the majority of time had mild effects it may give a distorted view if all these animals are categorised as 'moderate'
- Difficulties in recording severity for animals which have a phenotype that pre-disposes them to stress and as a result causes some to suffer unpredictable, not yet witnessed, but fatal seizures – animals are found dead in the cage
- Animals undergoing surgery in moderate category. If the wound becomes infected, the animal is killed. Would this be regarded as 'substantial' severity?

One respondent suggests that these uncertainties would lead to "an understandable tendency to downplay animal suffering".

#### **Other points for consideration**

Points/areas mentioned that might need further consideration include:

- Wild animal studies, where intervention is minimal (e.g. taking a single feather for identification of a bird), and other studies where adverse effects could be argued to be so mild as to be 'non-existent'
- Difficulties of dealing with GA animals – particularly 'no effect' groups
- FOI implications of retrospective reporting of severity in the public domain
- Implications for complexity of Returns form – e.g. this plea from the heart of a University respondent:

Please do not make this one more variable that we have to take into account when filling out those already fiendishly complicated annual statistics forms. If we have to report it, please make sure that it is just one figure at the end (e.g. 'of the 200 mice used, 180 experienced mild effects, and 20 moderate') and not '6 wild-type mice brought from a commercial supplier that underwent GA with recovery for reason code B79 had mild' etc."

#### 4. Possibility for predicting severity in advance, then reporting ‘exceptions’

Some of those who express concern about the volume of work that retrospective reporting of severity might bring seem to assume that this would necessarily require detailed reporting of all adverse effects (however slight) for all animals used. However, it is possible that in practice recording could be much simplified.

In protocols with mild severity limits, all animals should experience, at worst, mild effects. In moderate and substantial severity limit protocols, and depending on the nature of the work involved, it may also be possible to predict in advance of a study the category of severity of adverse effects that a given animal (or group of animals) will experience. E.g. for a ‘moderate’ protocol involving five treatment groups, it might be possible to predict that four treatment groups will experience only mild effects, but that one group is likely to experience moderate effects. If such predictions are possible, the process of recording actual severity experienced could then be reduced to recording only those animals which deviate from such expectations.

In light of this reasoning, the questionnaire asked PPLs whose licences contain moderate and substantial severity protocols how frequently they are able to predict the category of severity of adverse effects that the animals will experience.

Overall, around three quarters of a total of 132 respondents (74%, N = 98) say that they can ‘usually’ predict the severity of adverse effects in the moderate and/or substantial severity protocols they use. Nearly 1 in 5 (19%, N = 25) say that they can do this ‘occasionally’; and 7% (N = 9) say that they can ‘hardly ever’ predict in this way. In addition, 2 further respondents (one from a university, one from a RI) say that they can ‘usually or occasionally’ predict severity; and one (from a RI) says that they can ‘usually or hardly ever’ predict. These figures are broken down by type of establishment in Table 8a below.

**Table 8a: Ability to predict category of severity in advance, for moderate or substantial protocols**

**Q6** *In the moderate and/or substantial protocol(s) you use, how accurately\* are you able to predict in advance of a study what category of severity of adverse effects the animals are likely to experience (i.e. which groups of animals used in a protocol with a moderate severity limit will actually experience mild and which will experience moderate effects; and/or which groups of animals used in a protocol with a substantial severity limit will actually experience mild, moderate or substantial effects)?*

<b>Establishment type</b>	<b>‘Usually’ %</b>	<b>‘Occasionally’ %</b>	<b>‘Hardly ever’ %</b>
University	76	17	8
Research Institute	66	25	8
Industry	77	20	3
<b>OVERALL (N= 132)</b>	<b>74</b>	<b>19</b>	<b>7</b>

Rather few respondents offer explanations for their answers here. The information that is given about work falling into the ‘Occasional’ and ‘Hardly ever’ categories is summarised in Table 8b, overleaf.

\* Noticed (too late) that the question does not really match the answers! ‘Frequently’ would have been better.

**Table 8b: Examples of work involving substantial or moderate protocols for which severity can be predicted ‘occasionally’, or ‘hardly ever’**

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***‘Occasionally’ predictable examples:***

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Much work is fundamental therefore a best guess is all that can be applied to the prediction

GM mice whose phenotype predisposes to stress seizures which can be lethal but are hard to predict

The point of the experiment is to evaluate whether a particular intervention (pharmacological or molecular manipulation of host/pathogen) might be protective - hence must assume we cannot predict outcome.

Behavioural genetics: The adverse effects experienced in our experimental protocols are dependent on a multiplicity of parameters (genotype, genetic background, age, sex, cage conditions, colony health status to name but a few). Although we have recorded little in the way of adverse effects, we must be prepared for the eventuality that a change in any of the parameters may reveal such effects.

We breed ENU induced, spontaneous or transgenic neuromuscular mutants. It is not possible to predict whether these mutants will exhibit unexpected phenotypes (from normal to substantial level of severity) when bred into a different genetic background

GM. Usually predictable for lines currently being bred and studied; occasionally for lines newly created, or derived from back or inter-crossing (Usually/Occasionally)

Investigating totally new treatments, so very rarely possible to predict the number of animals which will suffer a particular level of severity until the first groups of animals have been treated

Assessment of vaccine formulations are initially based on antibody titres, however this may not reflect actual protection

Pharmaceutical safety assessment: can predict reasonably well for one month studies, because we have knowledge of the compound based on previous studies; but early candidate selection of dose ranging studies are almost impossible to predict

Genetic toxicology/safety assessment: prediction is less accurate for range finding, more accurate for the main study

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***‘Hardly ever’ predictable examples:***

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Surgery designed to produce heart failure, onset variable

Some of my protocols are to test biological material for presence of mouse pathogens or other agents that may cause unknown effects or substantial effects if they are present – but if I could predict I wouldn’t need to do the test!

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## **5. Other issues**

### **5.1 Subdivision of ‘moderate’ severity category?**

Mindful that some people argue that ‘moderate’ is too broad a severity category, the questionnaire also asked, “Would you find it helpful if the moderate category was sub-divided – e.g. into ‘upper’ and ‘lower’ moderate severity?”

154 respondents answered this question. 74% (N = 114) feel that the category should not be sub-divided; whilst 24% (N = 37) think that subdivision would be helpful. 2% (N=3) are uncertain, suggesting that sub-division could perhaps be helpful.

These figures are broken down by type of establishment in Table 9 overleaf.

**Table 9: Respondents' views on whether 'moderate' category should be sub-divided**

**Q8** *Some people argue that 'moderate' is too broad a severity category. Would you find it helpful if this category was sub-divided – e.g. into 'upper' and 'lower' moderate severity?*

<b>Establishment type</b>	<b>'Yes'</b> <b>%</b>	<b>'No'</b> <b>%</b>	<b>Possibly</b> <b>%</b>
University	28	72	0
Research Institute	17	79	3
Industry	19	74	6
<b>OVERALL (N= 154)</b>	24	74	2

Those who oppose sub-division tend to argue that this would over-complicate an already difficult-to-apply system and/or would not benefit animal welfare. Further comments mainly relate to the 'subjectivity' of the existing classification and the need for better guidelines and examples to illustrate how to assign the current categories.

## 5.2 Ways to improve the annual Returns procedure?

Finally, the questionnaire asked respondents, "Thinking more generally about the annual Returns procedure, are there any ways in which the codes or other aspects of the procedure could be modified to make it easier for you to report animal use under your project licence(s)?"

39 of the 101 licence holders who responded to the invitation to comment on this aspect suggest changes to the Returns process. These are summarised in Table 10 below.

A further 11 respondents appear to feel dissatisfied with the present process, but are uncertain what if anything might be changed – primarily because they find it difficult to envisage how the current complex procedure might be simplified. 51 respondents say that they have no particular problem with the Returns, and the remaining 67 licence holders who filled in the questionnaire did not comment on this final question.

**Table 10: Suggestions for improvements to the annual Returns procedure**

<b>Suggested change</b>	<b>N replies</b>
Make the codes more intuitive, and provide better guidance on what they mean. "Why call a rat an R2?"	8
Allow (easier?) submission on-line	7
Collect <u>only</u> data that is 'meaningful' in terms of animal welfare, and "remove codes that have never been reported"	7
Simplify and clarify reporting of GA animals ("confusing at best"). Suggestions: provide better guidance, find a better way of dealing with GA animals bred but not otherwise used (or remove requirement to report these) and merge GM and harmful mutant categories	6
Customise the Returns process, to fit specific areas of work more easily. "My kind of work doesn't fit well – the categories are usually 'other'".	3
Rearrange the hierarchy in the Returns form to avoid having to answer 'no' repeatedly (e.g. put the CITES question at the beginning)	2
Clarify particular areas: re-use (2); animal transfer and procedures crossing year ends	3
<u>Other</u> : help with difficulty of counting zebrafish; avoid changes year-on-year; get animal staff to fill in form on behalf of PPL	3

## LASA/APC Questions for project licence holders relating to Retrospective reporting of the actual severity of animal procedures

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**Note:** Herein, the phrase 'adverse effects' refers to all the adverse effects caused to animals by a protocol. The phrase is taken to encompass effects that are anticipated (and therefore listed in the relevant 19b) and those which are unanticipated; also effects that are 'required' for the purpose of the protocol (e.g. induction of disease) as well as unwanted side effects.

1. Ignoring any instances in which the severity limit is breached, do you currently record the adverse effects actually experienced by the animals in the protocols you use?

- Always  
 Sometimes  
 Never

**If you answered NEVER, please go to Question 5**

*If you answered ALWAYS or SOMETIMES, please continue.*

2. For which kinds of protocol do you record these actual adverse effects?

**Please mark all that apply:**

For protocols with a mild severity limit:  Always  Sometimes  Never  N/A

For protocols with a moderate severity limit:  Always  Sometimes  Never  N/A

For protocols with a substantial severity limit:  Always  Sometimes  Never  N/A

*Please comment further if you wish:*

3. When do you record these actual adverse effects?

**Please mark all that apply:**

- For all animals in the protocol(s) concerned  
 When the adverse effects look likely to approach the severity limit  
 When the adverse effects are uncertain or difficult to predict  
 When a protocol causes unanticipated or unusual adverse effects in practice  
 When a protocol involves novel techniques, or techniques that are new to my project team or the establishment  
 Other, *please state (or clarify the above):*

4. Do you record the above information in a way that would allow you easily to Return to the Home Office the number of animals used in each protocol by category of severity of adverse effects they actually experienced (i.e. mild, moderate or substantial)?  Yes  No

*Please comment further if you wish:*

5. Please indicate the severity of the protocol(s) included in your project licence(s):

**Please mark all that apply:**

- Unclassified
- Mild
- Moderate
- Substantial

**If you marked ONLY UNCLASSIFIED OR MILD, please go to Question 7**

If you marked MODERATE and/or SUBSTANTIAL please continue

Background to Question 6:

Of course, animals often do not reach the severity limit of the protocol in which they are used e.g. animals involved in a protocol with a moderate severity limit may experience only mild effects. This means that for retrospective reporting of the effects of moderate and substantial severity limit protocols it will not be sufficient simply to Return the number of animals used by protocol severity limit, because doing so will usually over-estimate the severity of adverse effects actually experienced by the animals.

Depending on the nature of the work involved, it may be possible to predict in advance of a study the category of severity of adverse effects that a given animal (or group of animals) will experience. E.g. for a 'moderate' protocol involving five treatment groups, it might be possible to predict that four treatment groups will experience only mild effects, but that one group is likely to experience moderate effects. If such predictions are possible, the process of recording actual severity experienced could then be reduced to recording only those animals which deviate from such expectations.

6. In the moderate and/or substantial protocol(s) you use, how accurately are you able to predict in advance of a study what category of severity of adverse effects the animals are likely to experience (i.e. which groups of animals used in a protocol with a moderate severity limit will actually experience mild and which will experience moderate effects; and/or which groups of animals used in a protocol with a substantial severity limit will actually experience mild, moderate or substantial effects)?

- Usually
- Occasionally
- Hardly ever

*Please comment further if you wish:*

7. How would/do you record the severity of adverse effects (mild, moderate or substantial) actually experienced by the animals in your protocols?

Do you foresee any particular difficulties in doing this?  Yes  No

*Please comment:*

8. Some people argue that 'moderate' is too broad a severity category. Would you find it helpful if this category was sub-divided – e.g. into 'upper' and 'lower' moderate severity?  Yes  No

*Please comment:*

9. Thinking more generally about the annual Returns procedure, are there any ways in which the codes or other aspects of the procedure could be modified to make it easier for you to report animal use under your project licence(s)?
10. To assist us in interpreting your responses, it would help if you would indicate the field(s) of work you are engaged in:

**Thank you very much for taking the time to respond.**