RESPONSE TO QUESTIONS 1- 5 of FOI REQUEST

1. The procedures indicated in the three articles were carried out under a project licence granted under the Animals (Scientific Procedures) Act 1986.
2. The licence was issued on 12th June 1998.
3. A draft application was received by the Home Office on 12 February 1998 and ASPI began its consideration of the proposals at this point. The formal application was received by the Home Office on 20 May 1998. There were 23 calendar days between the date the formal application was submitted and when the licence was granted.
4. The licence application was not referred to the Animals Procedures Committee (APC) for consultation.
5. The Animals Scientific Procedures Inspectorate did take account of relevant previous publications from the project licence applicant. There were ten references cited in the licence application itself. We have listed these below:

REFERENCES

1. Hainsworth R. Reflexes from the heart. Physiol. Rev 1991; 71: 617-658.
2. Al-Timman JKA, Drinkhill MJ, Hainsworth R. Reflex response to stimulation of mechanoreceptors in the left ventricle and coronary arteries in anaesthetized dogs. J. Physiol. 1993; 472: 769-783.
3. Drinkhill MJ, Moore J, Hainsworth R. Afferent discharges from coronary arterial and ventricular receptors in anaesthetized dogs. J. Physiol. 1993; 472: 785-799.
4. McMahon NC, Drinkhill MJ, Hainsworth R. Reflex vascular responses from aortic arch, carotid sinus and coronary baroreceptors in the anaesthetized dog. Exp. Physiol. 1996; 81: 397-408.
5. McMahon NC, Drinkhill MJ, Hainsworth R. Vascular responses to stimulation of carotid, aortic and coronary arterial baroreceptors with pulsatile and non-pulsatile pressures in anaesthetized dogs. Exp. Physiol. 1996; 81: 969-981.
6. Drinkhill MJ, McMahon NC, Hainsworth R. Delayed sympathetic efferent responses to coronary baroreceptor unloading in anaesthetized dogs. J. Physiol. 1996; 497: 261-269.
7. Mc Mahon NC, Drinkhill MJ, Hainsworth R. Absence of early resetting by coronary arterial baroreceptors. Submitted for publication.
8. Doe CPA, Drinkhill MJ, Myers DS, Self DA, Hainsworth R. Reflex vascular responses to abdominal venous distension in the anaesthetized dog. Am. J. Physiol. 1996; 271: H1049-H1056.
9. El-Sayed HM, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. Heart. 1996; 75: 134-143.
10. Shepherd JT, Hainsworth R. Future challenges: from introspection to prospection. Cardiovascular Reflex Control in Health and Disease ed. Hainsworth R, Mark AL. 1993; pp 491-510. WB Saunders Co, London.

- **Annex A** – a new document prepared by us to show the context through which our response to the specific questions in the request should be understood.

- **Annex B** -All relevant information from the file minute sheet for the project licence in question which formed part of the cost-benefit assessment

- **Annex C** - A typed copy of the project licence assessment form from the file held by ASPI

(1) What were the costs that were identified?
As all the surgery and invasive procedures were to be done under deep surgical anaesthesia under which the animal would remain until humanely killed, the main cost to the animals was the deemed to be the minor discomfort of inducing anaesthesia. For the one protocol in which there was preliminary blood sampling and an injection before the induction of anaesthesia, additional minor discomfort from these procedures was identified.

In order to ensure that the animal was completely unconscious and unable to feel any pain during the anaesthesia, particular attention was paid to the choice of agent and its analgesic properties. The choice of anaesthetic for cardiovascular studies has to take account of the effects anaesthetics have on the circulation and on respiration, and the anaesthetic proposed was determined the most appropriate for the work. However to ensure the animals felt no pain, the Inspector recommended that an analgesic was given in addition to the anaesthetic, to supplement the agent's limited analgesic effects.

(2) What were the benefits that were identified?
It was considered that the work would provide better scientific understanding of cardiovascular responses and the control of blood pressure. Significant advance in this area was expected from the project as

a) it had been fully peer reviewed and funded by the Medical Research Council,
b) the project holder was experienced in the field, highly regarded by the funding bodies, and well used to managing a programme of work involving regulated procedures,
c) the work was building on a body of published work by the group and the application showed good contemporary knowledge of the field, and
d) the subject was an important one in physiology and human pathology.

A longer term realistic prospect of improved therapy for control of blood pressure in animals and humans was also identified. Hypertension is recognised as a major human disease with important limitations to present therapy.

(3) Cost-benefit assessment
In analysing the proposal the Inspectorate considered that the programme was well justified and soundly designed, the facilities suitable, and rated highly the quality of the working hypotheses, the clarity and validity of the general aims and specific objectives, and the prospect of them being achieved in the course of the project. There were no non-animal alternatives for achieving these, and with the supplementary use of analgesic the potential suffering had been minimised.

The benefit was considered high and the cost very low.

(4) Cost-benefit assessment – Did the Inspectorate use of any particular calculation formula?
The 1986Act does not require that benefit outweighs cost. The Inspectorate did not use any calculation and has published its views on the inadequacy of quantitative approaches.

ANNEX B

PROJECT LICENCE MINUTE SHEET

1.4.98
I would appreciate the comment from [redacted] on (i) the effectiveness of alpha chloralose, used in the way stated, for the surgical procedures in this study, and (ii) the monitoring proposed to judge effectiveness of anaesthesia, and (iii) whether the cardiovascular parameters they are measuring can be reliably studied under alpha chloralose anaesthesia.

6.4.98
See file docket (3): in answer to [redacted] queries, I believe that α chloralose can be considered a suitable anaesthetic, if carefully monitored.

18.5.98
Application discussed with [redacted]. Notwithstanding [redacted] file note I have requested that opiate analgesia be incorporated into the procedures. Await final application.

9.8.98
This work is scientifically well justified and soundly designed. The model is recognised to be complex but valuable data has resulted from its use (as evidenced from previous publications) and review of grants (by MRC) using it. The main concern relates to the effectiveness of α chloralose as an analgesic during the surgical phase of the preparation of the model. [redacted] recognises these concerns and has taken steps to seek expert advice from anaesthesiologists. As a result the anaesthesia/ analgesia regime has been amended introducing the use of morphine sulphate during the early stages of the model preparation. [redacted] was asked for specialist comment on the model (see minute 6/4/98 and docket 3) and is content with the anaesthesia regime suggested subject to careful monitoring. As morphine will only be used on "most" occasions I will wish to be informed when, and why, it is not used. Given the potential sensitivity of the work frequent inspection/monitoring should be carried out.

RECCOMENDATION

1. Grant licence
2. Add Condition : " the intention to perform any procedure in which the administration of morphine sulphate at the dose specified in the project licence is NOT to be performed should be notified at least 72 hours in advance to the Home Office"

Docket 4) Licence issued, grant letter 12.6.98
Docket 5) Letter re: using replacement for morphine 17.12.98

8.1.99
Proposal to use alfentanil in place of morphine sulphate seems reasonable

15.1.99

Amendments discussed with licensee. Case made is reasonable and represents a refinement of the procedure.

Grant amendments, substitute pages dated 15.1.99

21.7.99
Tele-conv. with [redacted] Require rat and dog procedures to be separated. Further justification of rat model and how it refines the dog procedures requested.

16.9.99
Request to amend licence to use rats for some salt-loading experiments in place of dog. This represents a refinement of the protocol and uses fewer dogs. Dogs retained for complex perfusion studies.

Grant amendment, substitute pages drafted 9.9.99
Licence amended, letter sent 24/9/99

17.12.02
Amendments, Docket (14) considered. Addition of pigs is justified to evaluate a species to replace dogs on current authority. Techniques are the same and anaesthetic advice from NVS has been adequately incorporated. Intent is to refine methods and replace dogs. Acceptable

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* Blacked out spaces indicate where information has been redacted under section 40 (personal information) of the Freedom of Information Act 2000.

ANNEX C

PPL Assessment Form

PPL No: [redacted]

[For overview of project and details on purposes, species justification, referral and overall severity see RPR proforma]

	Rating (1 - 5, 1 high; * = suitable for rating) relevant option, tick (= Y) or N/A	Comments (if any)
Applicant		
* quality of work produced	1	Experienced cardiovascular physiologist and clinician.
* experience in this field	1	Highly regarded by MRC and funding bodies
* experience in another field	1	
experience of regulated work (PLH, DPLH, PILH)	1	
Deputy		
* quality of work produced	1	Main scientific researcher involved in [redacted]
* experience in this field	1	[redacted] group.
* experience in another field	1	
experience of regulated work (PLH, DPLH, PILH)	1	
First avail.		
* suitability of facilities for the work	1	
* suitability of staffing for the work	1	
Second avail. (Y or N)	N	
PODE avail. (Y or N)	N	
adequate description of PODE		
Background		
* adequacy of arguments for the proposed work	1	Arguments well proposed and accepted by grant
* potential value of the research	1	reviewers and funding bodies. Analysis of long term
* adequacy of literature review	1	blood pressure control may lead to improved therapy.
references support arguments	Y	Much literature quoted is applicants own. Highly
up-to-date references to others in the field	Y	regarded by MRC.
publications from previous project	Y	
good publications from applicant	Y	
Objectives		
* quality of working hypothesis(es)	1	Applicant has built on his own published work.
* clarity and validity of general aims	1	Important subject in physiology and human
* clarity and validity of specific objectives	1	pathology.
* feasibility within this project	1	
* importance of aims and objectives	1	
Benefits		
* better scientific understanding	1	Problems researched relate to man.
* insights into disease processes	1	
* improved therapy	1	
* safety	5	
* socio-economic	5	
* animal welfare or husbandry	5	
* other		
Plan		
up-to-date consideration of in vitro/ex vivo alternatives	Y	In vitro alternatives not available.
up-to-date consideration of less severe alternatives	N/A	
use of each procedure clear	Y	
plan valid for and should meet objectives	Y	
work appropriately staged	Y	
Design and analysis		
design includes proper controls. Group sizes	Y	From previously published work
proposed analysis appropriate for the design	Y	
evidence for competence in design and analysis	Y	
commitment to seek statistical advice	Y	
OECD guideline design or similar	N	

Adequacy of special justifications

* species	2	Primate might be better model but valuable data can
* second avail. and/or PODE avail.	N/A	be obtained from dog
* NMBs	N/A	
* substantial procedures	N/A	
* particular techniques	1	All techniques justified.
(indicate each techniques)	1	
	1	

Procedures

titles suitable	Y	Main concern over analgesic activity of alpha
severity limits appropriate	Y	chloralose has been addressed by incorporation of
* clarity of protocols and variations/repetitions	1	morphine sulphate into protocols
* adequacy of refinements	1	
* consideration of adverse effects	1	
* realistic controls and end points	Y	
non-Schedule 1 killing methods clear and supportable		
re-use legal, justified and within proper constraints	N/A	
transfer of animals legal and justified	N/A	
suitable species and stage development	Y	

Overall Severity

Estimated numbers by severity limit:

	Unclassified	Mild	Moderate	Substantial
rodents, rabbits, birds, reptiles, fish	160			
farm animals, deer, etc.				
dogs, cats equidae				
primates				
CITES species				
Total	160			
Decision on overall severity (tick column)	✓			

Factors considered in severity benefit analysis

* likelihood of valid and useful results	1
* prospect of stated benefits being realised	2
* areas of science/number of people affected, etc	1
* significance of objectives/seriousness of disease, etc.	2
* balance between benefit and severity	1

Comments on assessment of benefits likely to arise:

Increased fundamental knowledge on blood pressure control which may inform future research on therapy for hypertension

Comments on assessment of cost to the animals:

Procedures may involve some pre-treatment (19b3) but are mostly unclassified. Provided analgesia/ anaesthesia are adequate cost should be minimal. Use of morphine sulphate provides further assurance on control of any possible intra operative pain.

General or additional comments:

Inspector Signature: [redacted] Date: 09/06/1998

PPL ABSTRACT PROFORMA

PPL No [redacted]
Title Circulatory Control Mechanisms

PCD No (primary avail only) [redacted] **PODE**(Y or N) [redacted]

Permissible Purpose
Enter 1 in the box which represents the primary purpose and 2 in any other appropriate boxes

a	control of disease, ill health etc	
b	physiological studies	1
c	environmental protection	
d	advancement of biological or behavioural science	
e	education & training	
f	forensic enquiries	
g	breeding with harmful defects	

Referral

(Tick appropriate boxes)

APC: Cosmetics	
Tobacco	
Microsurgery	
Other	
Internal / second opinion	Y
External assessor	

Brief overview of project: (Maximum 2 sentences based on section 17, giving context and, most important why the work is worth doing)

Fundamental studies of cardiovascular and blood pressure control reflexes in anaesthetised dogs. May improve understanding of mechanisms of relevance to therapy and disease control in man.

Species Justification (Section 18)
(Tick appropriate box(es)

	Cat	Dog	Primate		Equine
			OW	NW	
Availability of background data		✓			
Required by regulatory authority					
Best model for human responses		✓			
Condition studies is species specific					

Other (specify)

Use of neuromuscular blockers (Y/N) N

Overall Severity

Substantial	
Moderate	
Mild	
Unclassified	✓

Inspector Signature: [redacted] Date: 09/06/1998