The need to refine the notion of reduction

Axel Kornerup Hansen[1], Peter Sandøe[2], Ove Svendsen[1], Birgitta Forsman[3] & Palle Thomsen[4]

[1]Department of Pharmacology and Pathobiology, Royal Veterinary and Agricultural University, Ridebanevej 3, DK-1870 Frederiksberg C, Copenhagen, Denmark [e-mail: akh@kvl.dk; os@kvl.dk], [2]Department of Animal Science and Animal Health, Royal Veterinary and Agricultural University, Groennegaardsvej 8, DK-1870 Frederiksberg C, Copenhagen, Denmark [e-mail: psand@coco.ihi.ku.dk], [3]Department of Medical Ethics, Lund University, Sölvegatan 9, S-223 62 Lund, Sweden [e-mail: Birgitta.Forsman@medetik.lu.se] and [4]Department of Experimental Medicine, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen N, Denmark [e-mail: pallet@expmed.ku.dk]

Summary

This paper challenges the widely accepted view that it is ethically preferable to reduce the number of live animals used in experimentation. The two main arguments in favour of reduction are presented and criticized. The first is the *welfare* argument, according to which reduction is an ethical improvement because it is invariably linked to a decrease in animal suffering. Against this, some cases are presented where either a decrease in the number of animals used leads instead to a significant increase in the suffering of the animals, or an increase in the number of animals used leads to improved animal welfare. The second is the *badness of killing* argument, according to which reduction is ethically desirable because it means that a smaller number of animals will be killed. It is argued that the ethical principle on which this argument is based, despite a certain intuitive appeal, does not cohere well with commonly held views about animal use.

In 1959, Russell and Burch inaugurated a new era of thinking by introducing the principles of reduction, replacement and refinement; the so-called 'Three Rs'. This lead to a considerable improvement in the welfare of laboratory animals. However, in spite of the obvious success of the 'Three Rs', critical reappraisal is now necessary to prevent the ideas of Russell and Burch from turning into pure dogmatism. Two arguments are presented in this paper: the *welfare* argument, and the *badness of killing* argument. We suggest that, of the 'Three Rs', reduction, at least, should no longer be considered a prime ethical goal.

The welfare argument

The welfare argument argues that reduction is ethically desirable because it leads to a decrease in animal suffering:

'The number of animals used in a given project needs to be minimized (reduction) while ensuring that the objectives of the study can still be achieved, typically, this will also reduce the sum of total animals suffering.' (Festing *et al*. 1998)

'The greater the number of animals used in an experiment, the greater will be the overall cost, in terms of animal suffering, of that experiment' (Smith & Boyd 1991).

However, a number of considerations tell against this argument.

The relation between suffering and animal numbers—the mathematical relationships

Experimenting with x_1 animals results in y_1 amount of suffering in the animals, but in a 'reduced' version experimenting with x_2 animals results in y_2 amount of suffering. So if

x_2 is less than x_1 and y_2 is less than y_1, the welfare of the animals is obviously improved and the argument is valid. Due to poor experimental design, poor experimental execution, insufficient training or inappropriate health status, the same procedure may have to be performed on more animals than necessary, because the variation was not adequately controlled (Festing 1991, 1994, 1995a). Reduction by controlling variation clearly goes together with an improvement in the ethical quality of animal research. However, if the number of animals (x) and the amount of suffering (y) are not independent of one another, the welfare argument may not be sound.

The statistical power of the experiment and the humane endpoint

Reducing experiments without refinement does not reduce variation and, therefore, the difference between the test groups must be increased if the power of the experiment is to be kept constant (Vølund 1994). It may be argued that reduction is ethically preferable to a smaller difference (Festing 1995b):

'Power can be increased by increasing the size of the experiment but, because this is expensive and ethically undesirable, the aim is usually to keep the experiment as small as possible... In some circumstances, the size of the treatment effect can be increased. For example, in toxicology it is usual to give high doses of the test compound, in order to induce a measurable toxic effect...'

However, an increased treatment effect often leads to increased discomfort or suffering in the animals. Many drug effects are dose-related; e.g. when cisplatin is used to induce neurotoxicity the main adverse clinical signs are nausea and vomiting. A smaller number of animals requires a higher dose to achieve significant neural changes, but the number of vomits per hour after cisplatin infusion rises with the dose (Ogilvie *et al*. 1989). From an animal welfare point of view it may be better to use more animals, if this reduces the number of vomits per hour in the individual animal. In the same way, if the experimental period is shortened, e.g. to prevent the animals being clinically affected in a carcinogenicity study, a higher number of animals may be needed to reach statistical significance. It may, therefore, be ethically preferable to use more animals in order to implement more humane endpoints. However, if the number of animals is reduced without raising the response of the individual, the statistical power of the study will be reduced. The latter type of reduction would not have been recommended by Russell and Burch (1959).

Laboratory animals used for routine production

Some laboratory animals are used for production rather than for experiments, e.g. for the production of antisera or for the propagation of tumour cells. If, for example, a human tumour is propagated in nude mice and a certain number of cells are needed, the larger the tumour in each mouse, the fewer the passages and the smaller the number of mice which will be used (Spang-Thomsen *et al*. 1986). It is more likely than not that procedures designed to give higher yields will result in greater inconvenience to each individual animal.

Re-use of animals

If animals, such as dogs or monkeys, were re-used for several different procedures, and so re-used more extensively than is the case today, the numbers of these species used would decrease substantially. This has, to some extent, been prevented by the *European Convention for the Protection of Animals used for Experimental and Other Scientific Purposes* (Council of Europe 1986) although there seems to be some flexibility concerning how this rule is interpreted. Countries which have not signed the European Convention may declare that a small number of, e.g. monkeys, have been used for research, when they have re-used the same animal for more than one harmful experiment. Also within the experiment it must be considered how many times an animal should be used. For example, Festing (1995a) describes an experiment which may be performed with

either 24 rats being bled on nine occasions or with 216 rats each being bled only once. Festing argues that a proper experimental design would have reduced the 216 rats to 72 rats and thereby shows how reduction and refinement go hand in hand, but it remains to be considered whether to use 72 or 24 rats. The 72 rats could be anaesthetized, bled and killed, while the 24 rats would have to be anaesthetized and recover eight times, and then anaesthetized, bled and killed. The latter procedure may cause severe stress, especially under certain types of anaesthesia (van Herck *et al*. 1991). If the discomfort after bleeding and anaesthesia is the only stress- or pain-causing part of the procedure, then the use of 72 rats leads to no suffering, while each of the 24 rats experience discomfort eight times. So, it may be ethically preferable to use 72 rats instead of 24.

Replacing individual animals

Although carefully planned, some experiments can have unacceptable consequences for individual animals and if those animals are killed during the experiment they will have to be replaced by other animals. It may be possible to give some analgesic treatment so that another animal will not have to undergo an introductory experimental procedure. However, the treatment may not adequately prevent discomfort in the animal. Also, the results received from the animal will be useless due to the false direction of the experiment if the animal has to be replaced later. The better option may, therefore, be to relieve the animal of pain by euthanasia and to use another animal, which raises the overall number of animals used in that study.

Considering the total amount of suffering and discomfort

It may be argued that, even though reduction can increase the suffering of individual animals, the total sum of suffering and discomfort it causes will decrease or at least remain constant. However, it must be borne in mind that the discomfort caused by some procedures, including some invasive ones, may be below the level at which the animal will register it as unpleasant. Furthermore, even if the procedure in question is unpleasant for the (greater number of) animals, it may nevertheless be unjustifiable to cause severe suffering in fewer animals—if this is the alternative. So, in theory there is both a lower limit, where the procedures are not prone to consideration, and an upper limit, where procedures may not be tolerated at all, no matter how many more animals have to be used to avoid the procedures.

The *'badness of killing'* argument

As should be clear from the above examples, there is often a conflict between reduction and refinement. If the goal of reduction does not seem to be desirable in these cases, there must be some other consideration in favour of it: e.g. that the simple use of laboratory animals—with or without suffering—leads to the killing of animals. Nearly all animal experiments conclude with the killing of the animals, so if the number of animals used in experiments is reduced, a smaller number of animals will be killed. Since, allegedly, the killing of an animal is bad, and should be avoided as far as possible, there is a good moral case for reducing the number of animals used in experiments—even when this does not lead to less animal suffering.

The previous argument relied on the principle that it is bad to cause animals to *suffer*. This argument appeals to a different ethical principle, that it is bad to *kill* animals. This argument leaves hardly any question that reduction will be in accordance with the principle, because reduction, in nearly every case, will ensure that a smaller number of animals are killed. Any challenge to the argument from the wrongness of killing will, therefore, have to focus on the ethical principle underlying the argument—that it is inherently bad to kill animals.

Philosophers interested in questions about animal welfare distinguish between two quite different ways of understanding the proposition that killing animals is bad. According to the *utilitarian* view such killing is not in itself wrong, while according to the *animal rights* view killing a healthy animal under normal circumstances is morally wrong. The utilitarian view determines that

the killing of animals is a problem only if it leads to animal suffering, or to a reduction in a pleasant, or otherwise worthwhile, animal life. Of course, killing an animal will often shorten the potentially good life of *that* animal. However, the animal killed may be replaced by another animal that would not otherwise have existed. This is frequently the case with farm animals:

'As long as a sentient being is conscious, it has an interest in experiencing as much pleasure and as little pain as possible. Sentience suffices to place a being within the sphere of equal consideration of interests; but it does not mean that the being has a personal interest in continuing to live. For a non-self-conscious being, death is the cessation of experiences, in much the same way that birth is the beginning of experiences. Death cannot be contrary to a preference for continued life, any more than birth could be in accordance with a preference for commencing life. To this extent, with non-self-conscious life, birth and death cancel each other out; whereas with self-conscious beings the fact that once self-conscious one may desire to continue living means that death inflicts a loss for which the birth of another is insufficient gain. . .'

'Given that an animal belongs to a species incapable of self-consciousness, it follows that it is not wrong to rear and kill it for food, provided that it lives a pleasant life and, after being killed, will be replaced by another animal which will lead a similarly pleasant life and would not have existed if the first animal had not been killed. This means that vegetarianism is not obligatory for those who can obtain meat from animals that they know to have been reared in this manner.' (Singer 1979)

Supporters of the *animal rights* view have argued that this utilitarian view fails because it does not respect the moral value of each individual animal. One of the most prominent adherents of this view, the American philosopher Tom Regan, defends the view in opposition to utilitarianism:

. . . unlike utilitarianism, the view in principle denies that we can justify good results by using evil means that violate an individual's rights—denies, for example, that it could be moral to kill my Aunt Bea to harvest beneficial consequences for others. That would be to sanction the disrespectful treatment of the individual in the name of the social good, something the rights view will not—categorically will not—ever allow.'

'. . . we are each of us the experiencing subject of a life, a conscious creature having an individual welfare that has importance to us whatever our usefulness to others. We want and prefer things, believe and feel things, recall and expect things. And all these dimensions of our life, including our pleasure and pain, our enjoyment and suffering, our satisfaction and frustration, our continued existence or our untimely death—all make a difference to the quality of our life as lived, as experienced, by us as individuals. As the same is true of those animals that concern us . . . they too must be viewed as the experiencing subjects of a life, with inherent value of their own. . .' (Regan 1985)

Those, then, who accept the rights view, and reject utilitarianism, deny that the harm done to an animal in an experiment can be justified by the good results of the experiments. And similarly, the killing of one animal cannot be compensated for by the fact that it is being replaced by another animal. As can be seen, there is an interesting conflict between a wholesale rejection of animal experimentation and an endorsement of the view that it is bad to kill animals. The utilitarian, of course, agrees with the rights view that if the potential future life of the animal would be a life worth living, the killing is in some sense a loss. The utilitarian believes, however, that this loss is fully compensated for if another animal takes the place of the dead animal. And, typically, in animal experimentation units, new animals will be purchased to replace those killed.

On reflection, some people may even deny that the killing of an animal is a loss in the sense just described. They may argue that

killing animals is a loss comparable with when we decide not to allow animals whose lives would be worth living to come into existence, e.g. by giving our cat a contraceptive pill. Since we do not consider it morally objectionable to prevent animals from coming into existence, we should also deny, according to this view, that it is morally objectionable to kill an animal—even if the animal is not replaced. Most people, however, will probably want to hold an intermediate view. On the one hand, along with the animal rights view, they will want to deny that there is nothing bad about killing an animal. But on the other hand, at least, in the case of production animals, they will accept a view more like the utilitarian's, and thus urge that if meat production animals lead a good (though short) life, and are transported and slaughtered in a humane way, then buying meat, milk and eggs is fully acceptable. However, they may be less comfortable with the killing of animals with which we have a closer relationship. For example, many people feel that cats should be neutered, because otherwise a large number of kittens will have to be killed. One way to reconstruct this middle position rationally is by saying that it is bad to kill an animal for no good reason, but that if there is good reason, there need not be anything bad about the killing. The production of food allegedly constitutes a good reason—although it must be observed that we do not need animal products in order to live.

The question remains whether there will not always be reasons that are at least as powerful in cases where the reduction of laboratory animal use is being discussed. The main reason for using animals in research is that it leads to valuable, and sometimes vital, information. A further reason, discussed in the previous section, is that the use of more animals will have a positive effect on animal welfare. It is hard to see how these can fail to constitute a good overall reason if the production of luxurious food is seen as a good reason. Given this, the use of the *badness of killing* argument turns out in such cases to be very questionable indeed.

Conclusion

Two claims have been defended in the previous two sections: (1) that the reduction in the number of animals used for experimentation will sometimes lead to more suffering in the animals; and (2) that when there is good reason to use more animals there is, in most people's view, nothing bad about the killing of these extra animals. Therefore, one can confidently pursue the goal of refinement, even if this means that more animals will have to be used. Equally, one need not have reservations about the goal of gaining valuable information through animal experimentation—as long as the welfare of the animals is not affected adversely.

Because the number of animals used for experimentation is such an easy thing to measure and understand, it has been seized upon by both opponents and advocates of animal experimentation. The former refer to the large number of animals used by experimenters, the latter present documentation to the effect that experimenters are using still fewer animals than before. Also, there is a clear commercial interest in cutting down the costs of animal experimentation. However, if the arguments of this paper are correct, those whose concern is for animal welfare should stop counting the bodies of animals used for experimentation, and instead should concentrate their attention on how the experiments affect the animals, and on whether the benefits gained by means of animal experimentation are worth the suffering and discomfort forced upon the animals.

References

Council of Europe (1986) *The European Convention for The Protection of Vertebrate Animals used for Experimental and Other Purposes*. Strasbourg

Festing MFW (1991) The reduction of animal use through genetic control of laboratory animals. In: *Animals in Biomedical Research, Replacement, Reduction and Refinement* (Hendriksen CFM, Koëter HBWM, eds). Amsterdam: Elsevier Science, pp 193–212

Festing MFW (1994) Reduction of animal use: experimental design and quality of experiments. *Laboratory Animals* **28**, 212–21

Festing MFW (1995a) Reduction of animal use and experimental design. In: *The World Congress on*

Alternatives and Animal Use in the Life Sciences: Education, Research, Testing (Goldberg AM, van Zutphen LFM, eds) pp 43–9

Festing MFW (1995b) Reduction in animal use 35 years after Russell & Burch's *Principles of Humane Experimental Technique. Alternatives to Laboratory Animals* **23**, 51–60

Festing MFW, Baumans V, Combes RD, *et al*. (1998) Reducing the use of laboratory animals in biomedical research: problems and possible solutions. *Alternatives to Laboratory Animals* **26**, 283–301

Ogilvie GK, Moore AS, Curtis CR (1989) Evaluation of cisplatin-induced dogs with malignant neoplasia (1984–1987). *Journal of the American Medical Veterinary Association* **195**, 1399–403

Regan T (1985) The case for animal rights. In: *In Defense of Animals* (Singer P, ed). Oxford: Basil Blackwell, pp 21–5

Russell WMS, Burch RL (1959) *The Principles of Humane Experimental Technique*. Springfield: Charles C. Thomas

Singer P (1979) Killing humans and killing animals. *Inquiry* **22**, 145–56

Smith JA, Boyd K (1991) *Lives in the Balance—The Ethics of Using Animals in Biomedical Research*. Oxford: Oxford University Press

Spang-Thomsen M, Clerici M, Engelholm SA, Vindeløv LL (1986) Growth kinetics and *in vivo* radiosensitivity in nude mice of two subpopulations derived from a single human small cell carcinoma of the lung. *European Journal of Cancer and Clinical Oncology* **22**, 549–56

van Herck HV, Baumans V, de Boer SF, van der Gugten J, van Woerkom AB, Beynen AC (1991) Endocrine stress response in rats subjected to singular orbital puncture while under diethyl-ether anesthesia. *Laboratory Animals* **25**, 325–9

Vølund AA (1994) Experimental design and statistical evaluation. In: *Handbook of Laboratory Animal Science*,Vol. 1 (Svendsen P, Hau J, eds). Boca Raton: CRC Press, pp 203–29