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Original article

The *RETHINK* project
Minipigs as models for the toxicity testing of new medicines and chemicals: an impact assessment

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ABSTRACT

The objective of the *RETHINK* project was to evaluate the potential impact of toxicity testing in the minipig as an alternative approach in regulatory toxicity testing that can contribute to the replacement, refinement and reduction of animal testing (3Rs). Minipigs are strains of domestic pigs that are markedly smaller than farmyard varieties, and thus better adapted to laboratory housing. The pig closely resembles man in many features of its anatomy, physiology, biochemistry and lifestyle. In particular, the cardio-vascular system, skin and digestive tract are considered to be very good models for man. Because of these similarities the toxic effects of chemicals and drugs in pigs may resemble the effects in man more closely than do some other commonly used laboratory animals. The pig also has some features that make it a very practical model for laboratory studies. Finally, being a food animal, testing in the minipig may be more acceptable to the public than animals such as dogs or monkeys. Expert study groups (Working Groups) were assembled to review five different areas relating to the use of minipigs in regulatory safety testing: ethical issues, welfare and animal care, development of new medicines and chemicals, safety testing issues and emerging technologies in safety testing. Their conclusions are presented in the articles of this special issue. The *RETHINK* project was funded as a Specific Support Action under the European Community 6th Framework Programme.

The *RETHINK* project, with the objective to evaluate the potential impact of toxicity testing in the minipig as an alternative approach in regulatory toxicity testing that can contribute to the replacement, refinement and reduction of animal testing (3Rs), was funded by European Community under the 6th Framework Project as a Specific Support Action (SSA).

This project provided a timely opportunity to review the minipig as an animal model in toxicology. The use of the pig in regulatory safety testing is not new. At the time that the legislative requirement for safety testing of new drugs was first introduced the pig was already considered to be one of the number of species that could offer an appropriate testing model. It is frequently stated that the pig is similar to humans in terms of anatomy and physiology and biochemistry, and the similarities render the pig an attractive model for biomedical research in general and toxicology in particular. Recent review articles have examined the role of the pig and/or minipig in toxicity testing (Lehmann, 1998; Gad, 2000; Svendsen, 2006; Nunoya et al., 2007).

Minipigs offer further advantages in terms of practicality, being bred to a manageable size for easy manipulation in the laboratory. The reduced size of these animals can also bring benefits in terms of reduced housing and husbandry costs. Numerous breeds of minipigs are available, including Sinclair, Yucatan and Hanford breeds in the USA and Ohmini, CLAWN and NIBS breeds in Japan (discussed in Nunoya et al., 2007).

In Europe, the best established, most widely used and best characterised breed is the Göttingen minipig. This breed originates from an initiative at the University of Göttingen in the 1960s and this breed is now produced commercially in Denmark. It is the only minipig that is produced on a large scale in Europe. In consequence, the Göttingen minipig was the minipig breed of reference for the *RETHINK* project.

The *RETHINK* project had the objective to evaluate the potential impact of toxicity testing in the minipig as an alternative approach in regulatory toxicity testing that can contribute to the replacement, refinement and reduction of animal testing (3Rs). The project arrives at a time when the regulatory toxicologist works in a turbulent environment. On one side, animal rights extremists denigrate the value of regulatory safety testing while societal pressures favour reduced testing in whole

The opinions expressed in this paper are those of the authors and not necessarily those of the organizations they represent.

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animals and greater emphasis on *in vitro* (or *in silico*) approaches. On the other side, new technical approaches are enriching our understanding of toxicological mechanisms. Toxicogenomic studies are providing rich and interesting data on (patho)physiological responses to chemicals and drugs that go far beyond what has previously been available. And from within the profession of toxicology, new initiatives look beyond current testing paradigms, and envisage radical new approaches for the toxicology of the future (National Research Council, 2007). It is therefore a highly propitious time to review the role of the minipig in toxicity testing, and to include an orientation of this review to the issues that are currently under debate, namely the role of animal testing, and the need for animal welfare, as well as the toxicology of the future.

The stated objective of the project raises numerous questions, such as: Are the animal welfare needs of minipigs well understood? Does the minipig provide scope for the reduction, refinement and replacement of animal experimentation? What economic impact or other consequences (favourable or unfavourable) will minipig testing have for the development of new medicines and chemical products? Is the use of the minipig scientifically justified and sufficiently validated? Is there a role for the minipig in replacing other non-rodent models like the dog and monkey? Is the minipig adapted to new and emerging technologies that will have a significant impact on regulatory toxicology? We categorised these questions in to five different areas: (i) ethics (ii) animal welfare, (iii) new medicines and chemicals development, (iv) safety testing issues and, (v) genomics and emerging technologies. Expert Working Groups (WG's) were set up in each of these areas, and have prepared the articles that constitute the final product of the *RETHINK* project (Webster et al. (2010-this issue), Ellegaard et al. (2010-this issue), van der Laan et al. (2010-this issue), Bode et al. (2010-this issue), Forster et al. (2010a,b-this issue), Simianer and Köhn (2010-this issue), Forster et al. (2010b-this issue)). In these articles the Working Groups have reviewed available information on their topics, have summarised the relevant knowledge-base and have drawn conclusions with regard to the objectives of the project. In addition they have identified any gaps in knowledge where further research is required, and technical gaps (e.g. availability of porcine reagents) presenting obstacles to the use of minipigs. They have commented on any specific issues that are raised, and have formulated recommendations regarding the use of minipigs in toxicity testing of new medicines and chemicals and their contribution to the replacement, refinement and reduction of animal.

The articles that follow aim to provide answers to questions such as the scope for application of 3Rs in minipigs, the welfare needs of minipigs, implications for development of new medicines and chemicals, the role of minipigs in toxicology testing strategies and proposals for initiatives to fill gaps in knowledge or technical gaps. The *RETHINK* project was designed and intended, not as a theoretical exercise, but to as an essential step towards the definition of strategies and future actions to exploit the potential of the minipig model in more efficient toxicity testing and more ethical animal experimentation.

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