

## RDA Memorandum – Growing Organs in Animals

The Council on Animal Affairs (RDA) has conducted an inventory of the issues around the growing of human organs, tissues and cells in animals for transplant purposes. This memorandum highlights the considerations that apply to the use of animals for this purpose and was partly drafted to support the social dialogue on 'Growing human organs, tissue & cells in animals', which was organised in late 2021 by a consortium led by the Rathenau Institute and NEMO Kennislink. The Council does not take a position in this memorandum.

To crystallise the considerations, this social issue was approached in stages. Is the growing of human organs in animals a possible solution to a genuine problem? What impact would this application have on animals? And how should this impact on animals be weighed against the goal of the application, given current social and ethical perspectives on animals?

### Donor shortage

There is an ongoing shortage of donors in the Netherlands. Evidence of this growing trend can be seen in the number of patients on waiting lists for donor organs. At the end of 2020, this number was 1,257. Although attempts are being made in the Netherlands to increase the number of donors, including through an active donor registration system set up in 2020, the current shortage is not expected to disappear in the short term. This means the physical and mental suffering of patients will continue and deaths will occur. Because special interests are at stake for humans, people are looking at possible alternative solutions for the donor shortage. One of those potential alternatives is to transplant human organs into patients from human-animal chimeras.

### Growing organs in animals to reduce distress for humans

Chimerism is when cells with different genetic backgrounds appear in a single individual. Chimeras can also be created artificially. When human stem cells – cells that have the ability to develop into different types of tissue – are inserted in an animal embryo, a human-animal combination can be created. Genetic modifications could be used to ensure that only a specific tissue or organ of human genetic origin develops in the animal

embryo. The embryo can continue its development inside an animal surrogate mother. When a viable human-animal chimaera is born, in theory, the target organ can be removed from the animal and transplanted into the human patient.

### *Is this an effective application?*

One advantage of organ transplants using human-animal chimaeras is that the cultured tissue would contain the genetic code of the target patient. Although there have been relevant scientific developments, for example in the area of gene editing, organ transplants using human-animal chimaeras are not yet within the realm of technical possibility. There is also considerable uncertainty about the effectiveness and safety of this potential application. Furthermore, there are questions about the real zoonotic risks – including the transfer of endogenous retroviruses – from transplanting organs from animals to humans. At the moment, it is still not certain whether and how organ cultivation might contribute to solving the social problem of a shortage of organ donations.

## **The effects on the animal**

### *Impact on the welfare of the donor animal*

What the effects will be for the welfare of the donor animals is a question that does not have a simple answer. Welfare impacts will arise as a consequence of the genetic modification of the animals and from the conditions in which human-animal chimaeras are kept.

Genome modifications using gene-editing techniques will be necessary for the development of suitable human-animal chimaeras. Although gene-editing techniques are much more precise and efficient than previous genetic modification techniques, there are still certain risks associated with them, including health risks. Artificially breaking down the barriers between animal species in chimaeras is also associated with premature embryonic mortality, miscarriage and malformations.

The housing system used for the donor animals could also affect their welfare. There is uncertainty about the living conditions that would apply to donor animals in an organ transplant chain. The animals would be valuable, and keepers would thus have considerable motivation to treat them with care. However, because the animals would have been bred strictly for human purposes, and those purposes would impose requirements on how the animals are looked after, the conditions are not expected to be

optimal for the animals. It is questionable whether animals bred for organ transplantation would be allowed to exhibit their natural behaviours. Indeed, to prevent the valuable donor animals from being exposed to pathogens, it is conceivable that they would have to be kept under highly controlled conditions, as is the case for SPF (Specific Pathogen Free) animals. Living in social groups with other members of their species is probably also a risk that would have to be eliminated. For a social animal like a pig, which has been proposed as a possible donor animal, an isolated life would be a cause of great distress. Possible medical interventions to achieve immunosuppression in the donor animal would also have an impact on the animal's welfare. In addition, it is inherent in the system that the animal would be killed following the surgical removal of the donor organ.

#### *Impact on the welfare of animals in the research phase*

In addition to the effects on the donor animals, when weighing up the competing interests, we must also look at the animals that would be involved in the *development* of such a practice, from the perspective of the animals themselves. Research into organ transplants using human-animal chimaeras will unavoidably be accompanied by large amounts of animal testing. Such animal testing is necessary to answer questions about effectiveness, safety and welfare in relation to organ transplants from human-animal chimaeras. The laboratory animals used in the research phase will derive no benefit whatsoever from the experiments, but will experience distress.

#### *Violation of the integrity of the animal*

This application would also involve a violation of the integrity of the animals concerned. Integrity encompasses the species-specific 'wholeness' and completeness of an animal and its ability to function independently, according to its nature, in an environment appropriate to its species. To create human-animal chimaeras for organ transplant purposes, genetic modification techniques would be used to alter the animal's genome in the embryonic phase in such a way that it would no longer develop a specific organ itself. This would clear the way for the human stem cells inserted into the animal embryo to grow into the target organ, which would violate the species-specific integrity of the animal.

## **Moral considerations**

It is clear from the above that, for humans, there is a genuine problem involving compelling interests. However, it is still highly uncertain whether and, if so, how growing organs in animals could contribute to solving this problem. The Council also notes that the use of laboratory animals in the research phase and the use of animals for the application would have a negative impact on the welfare of the animals concerned. The level of the welfare risk cannot yet be quantified in detail. The acceptability of using animals to grow organs in human-animal chimaeras depends on how we weigh the animals' distress against the relevant health interest. In addition, there is a degree of uncertainty, both on the part of the animal (degree of distress) and on the part of humans (feasibility, effectiveness and safety) that will have an impact on the consideration.

### *Goal of the application*

On one side of the equation is the health interest – the goal – of the application. Accordingly, it is appropriate to clearly identify the various objectives of organ transplants from human-animal chimaeras through a wide-ranging discussion. One goal of transplanting organs from human-animal chimaeras to patients is to increase the chances of survival of people who are seriously ill. But is saving human lives the only objective for organ transplants from human-animal chimaeras? Or might such transplants also be used to increase people's quality of life? Clarity about the objectives is required in order to evaluate the proportionality of the violation of the welfare and integrity of the animals concerned when weighing up the competing interests.

### *The moral position of animals*

On the other side of the equation is the distress caused to the animals involved. The weight citizens give to negative effects on animal welfare depends on how they view and relate to animals. Their moral starting point thus determines how the social issue is approached. There is a diverse range of views in society about the moral status of animals. If an animal is seen as an object with only instrumental value, then the use of that animal does not present a moral issue. At the other end of the spectrum, animals are recognised as moral subjects. Causing distress to animals or violating their integrity for a purely human goal would not be acceptable. There are also many views in between. Based on these views, the use of animals for human purposes would only be acceptable under certain conditions.

In the Netherlands, the social position of animals is enshrined in the Animals Act (*Wet dieren*). This Act recognises the intrinsic value of animals. The intrinsic value of an animal refers to an inherent value that is unrelated to the animal's potential to be of use to humans. The interests of the individual animal must therefore be taken into account when weighing competing interests. The capacity of certain animals to experience pleasure and pain is a reason to consider their welfare in our dealings with animals. In addition to welfare, inherent in the recognition of the intrinsic value of animals are concepts such as animal integrity and the value of life.

### *Uncertainty*

The next question is how much uncertainty we would be willing to accept in the equation. If the use of animals is found to be acceptable under certain conditions, uncertainty with regard to the feasibility, effectiveness and safety of the application, as well as with regard to the distress that is expected to be caused to the animals concerned, will play a role. A high degree of uncertainty makes it difficult to weigh the competing interests. In such a situation, the precautionary principle could be applied. Under this principle, in situations of uncertainty, not only must the foreseeable consequences be taken into account, but the potentially far-reaching consequences for the parties involved must also be considered. Based on the precautionary principle, the potentially profound negative impact on the welfare of large numbers of animals can be advanced as a legitimate reason to refrain from the application as a whole, even if we consider the use of animals to be acceptable subject to conditions.

### **The changing relationship between people and animals in the Netherlands**

Scientific insights into the distress that would be felt by animals in an organ transplant chain would eliminate uncertainty, thus making it easier to weigh the competing interests, but this would not lead to a consensus about the acceptability of the application. As discussed earlier, the moral status accorded to animals has a major influence on how we assess the application. In this regard, it is relevant to point out that the position of animals in society is dynamic. Multiple views on animals exist side by side and regularly change to reflect the spirit of the times. In 2018, the RDA conducted a public survey to examine the attitudes of Dutch people towards animals. The survey revealed that animals are very close to the hearts of the Dutch population. In the report it released on the topic, *The State of the Animal*, the Council argued that the relationship with animals has changed over the years, with people increasingly moving away from stewardship towards a partnership with animals. The Council believes it is important for

this trend to be taken into account in the overall dialogue about allowing human organs to be grown in animals. The setting up of yet another animal husbandry system could lead to public opposition, due to the position that animals have acquired in society. After all, the social movement towards animals as intrinsically valuable entities (and away from animals being seen as 'instruments') would be difficult to reconcile with the establishment of a new animal production system.

## **Subsidiarity**

As we have seen, there is a range of objections to the use of human-animal chimaeras to reduce the shortage of donor organs. When we consider using animals to solve a human problem, it is important not to lose sight of the alternatives. Using a pig to save a human life appears to result in a reduction of the overall distress. But a safe and effective alternative that does not use animals would, on balance, lead to a more positive outcome. The next question then is whether less risky and/or less ethically problematic alternatives could be developed to reduce the shortage of donor organs.

In recent years, researchers have made significant steps in the areas of *in vitro* tissue culture (organoids) and bioprinting. An additional benefit of investing in these *in vitro* alternatives is that the zoonotic risks would be eliminated. The amount of research funding is not infinite, and money that is currently being invested in a certain direction is no longer available for the development of alternatives. It would therefore be appropriate to assign a higher priority to research into alternatives that would involve less suffering for animals.

## **Conclusion**

Given the organ shortage in the Netherlands, we are facing a problem that is associated with considerable patient suffering. Human-animal chimaeras could potentially contribute to alleviating the current shortage, but there is still a great deal of uncertainty about the feasibility, safety and effectiveness of the application. There are also a number of issues concerning the welfare and use of animals for organ and tissue culture, both in the research phase and in the final application. Negative impacts on animal welfare could arise as a consequence of genetic modifications, the conditions under which the animals would be kept and medical and surgical interventions. The application would also involve a violation of the integrity of the animals concerned, and the animals would be killed in order to achieve the goal of the application. These effects – on both the laboratory animals and the donor animals – must be taken into consideration in discussions. How an

individual relates to animals has a significant influence on the moral weight they give to this distress in animals. In this respect, the Council observes that the way in which animals are valued by Dutch society is increasingly shifting from a view of animals as tools to animals being seen as intrinsically valuable entities. In addition, as part of the wide-ranging discussions to come, other promising alternatives – which would not require the use of animals – must be publicised more widely, to facilitate the careful consideration of the competing interests.