QALY as a supporting factor for animal model selection in animal research

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Abstract

Given the utilitarian basis of animal research legislation (we focus on the German and Swiss Animal Welfare Acts, here, but acknowledge European animal research regulations, namely the Directive 2010/63, too), it seems plausible to suggest further utility-based tools for decision-making in animal research. The "Quality-Adjusted-Life Years" (QALY) is a measure in medicine and public health, originally used to compare different approaches in a health care system (population-based) or different interventions for an individual patient (individual-based) in clinical decision-making regarding the outcome for the patients (and, consequently, their cost-effectiveness). The basic idea of QALY is the integration of the expected remaining quantity and quality of life for a patient, whereby quantity is measured in years and quality in a health state value between zero (death) and one (perfect health), occasionally also including negative values for states worth than death. In animal research, the selection of animal models is currently based on different ethical, legal, and practical criteria, such as: preferring non-vertebrates over vertebrates, fish over mammals, less sentient over more sentient animals, well-established model organisms over less conventional species, choosing animals "lower on the evolutionary scale", natural hosts, or those animals who are easier to handle. From an animal ethics perspective, in contrast to the suffering inflicted during experimental procedures, the loss of lifetime for the individual animal when being used for a research study is currently not taken into consideration. Here, we want to suggest implementing QALY in animal research (QALYAR) as a way of including this criterion as a morally relevant aspect for the model selection in animal research. Like in the QALY calculation, a health state value should be attributed to each phase of the potential laboratory animal's life. QALYAR can, accordingly, be influenced not only by the choice of animal species (or breeding line) but also by the animal's age at the time of the experiment, by different solutions to take care of animals after the experiment, and by the refinement of all human-animal-interaction in the animal's life. An adaptation of the original parameters to calculate QALY in human medicine would have to be discussed for QALYAR in detail.

Laboratory animal model selection in the law

Despite the plurality of current approaches in animal ethics and despite the complexity of human-animal relationships, most animal welfare legislation is still based on utilitarian assumptions. On the one hand, the legal implementation of concepts like the intrinsic value (Article 1.3 Dutch Animal Welfare Act) of animals, animal dignity (Chapter 1, Article 3 Swiss Animal Welfare Act), or the protection of animal life (Section 1 German Animal Welfare Act) points towards gradual changes in animal welfare law. On the other hand, when it comes to concrete, specific regulations of human-animal interactions, they predominantly include a utilitarian weighing of animal welfare against other (human) goods and preferences.

In animal research, the process of animal model selection is only vaguely framed and guided by most animal welfare legislation. By "animal model" we refer here mainly to the species of the animal but also to breeding lines or models for particular diseases or genetic properties. Animal model selection can be

crucial for several aspects of animal research such as effort, outcome, validity and translational power of a study (D'Angelo *et al*., 2022),. The EU Directive 2010/63 prescribes the selection of the species "with the lowest capacity to experience pain, suffering, distress or lasting harm" (13). While the Swiss Animal Welfare Law dictates the choice of species which are lowest on the evolutionary scale (Section 20b) (without compromising the scientific outcome of the study), the German Animal Welfare Act asks to pick that type of animal that would suffer the least from the experimental procedure (Section 7a (2)), presenting a precision of the EU directive by focusing on the context (suffering *from the experimental procedure*) instead of inherent properties (the *species with the lowest capacity*...) of the animal. Further selection criteria that are mentioned or implied in Western Animal Welfare legislation but will not be discussed in detail, such as: preferring non-vertebrates over vertebrates, preferring fish over mammals, preferring less sentient over more sentient animals, preferring well-established model organisms over less conventional species, early developmental stages over adult animals, choosing natural hosts, or those animals who are easier to handle.

Lifetime wellbeing as a criterion in laboratory animal model selection

From an animal ethics perspective, in contrast to the suffering inflicted during experimental procedures, the loss of lifetime for the individual animal when being used and killed for a research study, and the loss through lifetime being spent in a non-preferable state are currently not taken into consideration. Here, we want to suggest a way of including these criteria as morally relevant aspects for the model selection in animal research. Before explaining the method of attributing quality-adjusted life years to animal life, we want to make the assumptions explicit that, despite being far from undisputed in the animal philosophy discourse, will be taken as given for the purpose of our argument, here. Firstly, and broadly accepted in both science and philosophy, we assume that animals have preferences for certain states in life and, secondly, that we have means to access those preferences at least to some extent. Furthermore, we adhere to the view that animals have a lifetime wellbeing. We will provide examples for measuring tools later on. Thirdly, we assume that death means a harm to animals, at least in a simple sense of the deprivation account of animal death, that is, the animal is deprived of future chances to experience moments in life (Delon, 2023). Based on these assumptions it makes sense to compare the lifetime wellbeing of animals' lives and compare the quality of different life scenarios with earlier and later times of death.

QALY as a concept

The Quality-Adjusted-Life Year (QALY) is a measure in human medicine and public health, originally used to compare different approaches in a health care system (population-based) or different interventions for an individual patient (individual-based) in clinical decision-making regarding the outcome for the patients (and, consequently, their cost-effectiveness). The basic idea of QALY is the integration of the expected remaining quantity and quality of life for a patient:

"Conceptually based in expected utility theory, the QALY rests on the assumption that preference-weighted values may be attached to specific health states relative to the time spent in those states. Because the QALY incorporates both quantity and quality of life, it therefore provides a reasonable estimate of the amount of quality time (i.e., health benefit) an individual may experience as a result of a particular health program or intervention. Furthermore, comparisons between programs or interventions may be made both within a single disease and across different diseases. Consequently, the QALY has been widely used as an outcome measure in medicine, psychology, public health, and economics.

Calculation of the QALY requires various health states be assigned a value ranging from zero to one, with zero representing death and one representing ideal health. Health states considered worse than death (i.e., a health state valuation less than zero) can also exist and are assigned a negative value. In order to

determine the values of each particular health state, respondents are asked to rate them relative to one another, or using an anchor point such as death. Several methods may be used to ascertain valuations, including preference measurement techniques such as the standard gamble or time trade-off, or through the use of rating scales, such as the EQ-5D, Health Utilities Index, Quality of Well-Being Scale, and SF-6D." (Howren, 2013).

The transfer from human medicine to animal research obviously requires some adaptations and the purpose of the value shifts from an economic to an ethics angle. However, the core idea that quality and quantity of life could be integrated in a single value that can be useful in decision-making processes is comparable. We will briefly describe the steps towards a "quality adjusted life year measure for animal research" (QALYAR) in the following chapter.

QALYAR - QALY for animal research

Like in the QALY calculation, a health state value should be attributed to each phase of the potential laboratory animal's life. That includes the influences of living under laboratory conditions (e.g., limitations regarding movement and choice of social partners, boredom, being handled by laboratory staff, transportation, etc.), effects of genetic modifications (e.g., disposition for development of certain diseases), the duration and frequency of study participation and the extent to which the physical and mental health state are affected during the experimental procedure; but also the age and average life expectancy of the respective species and the animal's fate after the experiment. The QALYAR can, accordingly, be influenced not only by (1) the choice of animal species (or breeding line), but also by (2) the animal's age at the time of the experiment, by different solutions to take care of animals after the experiment, and by (3) the refinement of all human-animal-interaction in the animal's life. An adaptation of the original parameters to calculate QALY in human medicine would have to be discussed for animals in detail.

(1) The law (as well as societal norms) distinguishes between certain animal species at various points within the animal research legal framework. Following the EU directive 2010/63, the German Animal Welfare Act (German acronym TierSchG), and the Animal Welfare Regulation Governing Experimental Animals (German acronym TierSchVersV), specifically cover only vertebrates and cephalopods. Furthermore, certain regulations apply to dogs, cats and primates (e.g., TierSchG Section 4 No. 3, TierSchVersV Sections 8, 9, 23, 24, 28, 29). The reasons for making these kinds of categorizations can be interpreted as follows: The former regulations in a way try to take into consideration the different kinds of capacities to suffer, while the latter can be explained by a special kind of human–animal relation. Focussing on the first group, it can be stated that, in general, vertebrates and cephalopods are considered to be on a 'higher' level of evolutionary development and therefore have a higher capacity for suffering (by having developed the biological prerequisites for this). Given the pathocentric principle within the legal framework, a higher capacity for suffering constitutes a higher level of protection claims. This pathocentric claim behind these distinctions in law is taken into account in a special way by a QALYAR-approach: A QALYAR-value, which would be attributed to an animal here, would precisely take into account the ability of a being to suffer, as this is an essential factor in the calculation. In this sense, the requirements of the legal framework would be fulfilled by implementing the QALYAR-approach on the one hand and, on the other, would be very feasible in practice due to its (quasi-empirical) method. Of course, this claim is only valid under the assumption that calculating subjective mental status of beings is always limited. As subjective mental status are, epistemological speaking, exactly that: radically subjective. And accordingly, the empirical ascertainability of these states is always subject to epistemological limits. Nevertheless, it is possible to draw meaningful conclusions about subjectively experienced states — and some indications of this may even be empirically measurable under certain circumstances (e.g. certain physiological parameters).

A special effect should also be briefly mentioned here: a QALYAR-approach focuses precisely on the subjective quality of experiences of individuals, without making absolute statements about these qualities. But also without making normative statements about these qualities in comparison of different species to one another. To a certain extent, this takes into account the ethical principle that the individual well-being of a being should be central to the considerations (cf. e.g. Tom Regan).

(2) To begin with, a more general remark is to be made: there is something particular for the laboratory animal context which is absolutely different for the original applications of QALY. The animal individual is not the focus of the intervention, he is not the "patient" like in human or veterinary medicine, but a means to another end. Accordingly, it is not the main goal of animal research to promote laboratory animal wellbeing but rather a necessity amongst others. For those reasons, a high QAYLYAR value is, from an ethical point of view, something that should be taken into consideration when choosing model organisms, even though maximising QALYAR it is not part of the scientific agenda. Having said that, the QALYAR would be highly dependent on the animals' age in several respects. There are at least three different dimensions of animal age that could be considered (Persson *et al*., 2022).

Firstly, a research animal of old age might not be able to compensate for a treatment's side effect as easily as a younger one. It might also take her longer to recover or she might suffer from comorbidities. Her overall quality of life during a given treatment might accordingly be comparatively low and a longer duration in that stage would affect QALYAR negatively.

Secondly, an individual's remaining life expectancy is an important criterion to calculate the quality-adjusted life years in human medicine – and it should count in the same way for QALYAR. On the one hand, a short remaining life expectancy means an overall constraint for the value for QALYAR because the high-quality life-time that can be gained is very limited. On the other hand, a long remaining life expectancy means that (1) what the animal is deprived of if her life is taken early is a lot or (2) a long time of suffering under the conditions of living in a laboratory and being experimented on. As a practical consequence, one piece of advice in terms of QALYAR could be to prefer species with an overall low or very low life expectancy.

Thirdly, there is the idea of "fair innings" which "reflects the feeling that everyone is entitled to some 'normal' span of health (...) and anyone failing to achieve this has been cheated, whilst anyone getting more than this is 'living on borrowed time'" (Williams, 1997: p. 117). For lab animals, a reasonable "normal span of health" would have to be defined, as animal life under laboratory condition differs fundamentally from other animals' lives. A criterion for the choice of species could be if the respective animal has a normal span of health, if he can live his life to a comparatively large extent of the full potential. Here, the option of rehoming animals might come into play as an additional chapter of their life would be added.

(3) Two aspects of human-animal relations in the context of the choice of animal models should be briefly mentioned here. Firstly, an analytical argument: the choice of an animal model is often influenced or even determined by particular human-animal-relations. This can be exemplified by the fact that the legal framework provides special regulations for cats and dogs (see above). These regulations are often based on certain social norms and human-animal-relations. If QALYAR aspects are the guiding principle for decisions on the choice of an animal model, such exceptions or distinctions would ultimately be arbitrary and could not be used to justify preferential treatment for certain species solely on the basis of their particular human-animal-relations.

A more prospective thought should also be voiced: A refinement of human-animal-interactions (such as a phase of getting to know the animals prior to the start of a study) may also have a beneficial effect on the husbandry conditions of the animals and a QALYAR score would increase accordingly.

Conclusion

Any concept that focusses on the quality of animals' lives faces an inherent problem. It balances some calculated good in the future against a harm in the present. While humans can decide to endure some kind of pain or discomfort in the present (e.g. throughout a medical treatment) in order to experience some good (e.g. a beneficial health status) in the future, nonhuman animals cannot. As far as we know today, most animals lack this fundamental capability to free themselves from the constraints, the circumstances of the situation, the moment itself, to place themselves in relation to the circumstances, to reflect, and, consequently, to revise their (initial) judgement if necessary, i.e., to be able to change their mind. Animals, in that sense, are 'closely tied to the peg of the moment' (Nietzsche, 1999: p. 248). Animals experience their affections and inner states in a very direct and inescapable way. According to Bernard Rollin, "We must remember that an animal *is* its pain, for it is incapable of anticipating or even hoping for cessation of that pain" (Rollin 2011, p. 657). Taking this into account, a QALYAR-approach within ethical considerations in animal research always has to bear in mind, that there is an absolute maximum of negatively experienced conditions of an animal that categorically prohibits any forthgoing, even if there is a high probability of a high quality of life in the future. Thus, there are absolute limits of suffering of an animal in the present, regardless of the prospects of success in the future. (It is also the case that humans might suffer from the prospect of having a shorter life time than they had expected, whereas most nonhuman animals lack the awareness of their life expectancy and can, thus, not suffer from that prospect. Based on that, one can argue that shortening or not prolonging nonhuman animal life is less bad than shortening or not prolonging human life.)

Tools for the evaluation of animal quality of life resemble questionnaires that are used to assess the quality of life in human patients who are unable to self-report, such as small children or cognitively impaired patients, usually answered by proxies and known as OROs (obswerver-reported outcome measures) (Fulmer *et al*., 2022). The development of disease-specific assessment tools can be helpful for QALYAR calculation, as they are sensitive to the impact of particular diseases or treatments that can be an important part of laboratory research. Nevertheless, aspects like the specific circumstances of living under laboratory conditions, being handled, treated, and, in the end, if applicable, being killed if "humane endpoints" are reached, would have to be integrated in already existing tools to render them suitable in the cases of laboratory animals.

Furthermore, another limitation of the concept of QALYAR has to be mentioned, which is a problem of justification theory. QALYAR-approaches are ultimately based on a consequentialist, or more precisely: a utilitarian premise. And as such, the objections that are raised against utilitarian concepts should also be addressed here (Williams, 1973). These include, among others: problems in measuring happiness, unpredictability of consequences or the fundamental problem of violating individual rights.

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