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Article abstract

Despite the international 3Rs principles that recommends replacing, reducing and refining the use of animals in medical experimentation, it remains difficult to obtain funding in Canada for medical research that respects these principles, particularly with regard to replacement. This observation led our team to review the literature on the arguments for and against animal experimentation in the fields of oncology and radiobiology. This article presents a synthesis of these arguments. Using the method created by McCullough and colleagues to conduct critical reviews of the ethics literature, we analysed 25 texts discussing the arguments for and against animal experimentation in oncology and radiobiology. Six broad categories of arguments for animal experimentation and eleven categories of arguments against it emerged from our analyses. Furthermore, the arguments against animal testing are more convincing from both an empirical and normative perspective. Also, most arguments obtained are transferable in other fields of medicine. In addition to the literature review, a critical reflection was conducted and other arguments were discussed. It seems that a conservative culture persists in medical research, despite the scientific evidence and ethical arguments to the contrary.

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**ARTICLE** (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

# Animal Experimentation in Oncology and Radiobiology: Arguments for and Against Following a Critical Literature Review

William-Philippe Girard[a], Antony Bertrand-Grenier[b], Marie-Josée Drolet[c]

**Résumé**
Malgré les principes internationaux des 3R qui recommande de remplacer, réduire et raffiner l'utilisation des animaux dans l'expérimentation médicale, il reste difficile d'obtenir au Canada le financement de recherches médicales qui respectent ces principes, notamment en ce qui concerne le remplacement. Ce constat a amené notre équipe à faire une revue de la littérature sur les arguments pour et contre l'expérimentation animale dans les domaines de l'oncologie et de la radiobiologie. Cet article présente une synthèse de ces arguments. En utilisant la méthode créée par McCullough et collègues pour réaliser des revues critiques de la littérature en éthique, nous avons analysé 25 écrits discutant des arguments pour et contre l'expérimentation animale en oncologie et en radiobiologie. Six grandes catégories d'arguments en faveur de l'expérimentation animale et onze catégories d'arguments contre celle-ci sont ressorties de nos analyses. En outre, les arguments contre l'expérimentation animale sont plus convaincants d'un point de vue empirique et normatif. De plus, la plupart des arguments obtenus sont transférables dans d'autres domaines de la médecine. En plus de l'analyse documentaire, une réflexion critique a été menée et d'autres arguments ont été discutés. Il semble qu'une culture conservatrice persiste dans la recherche médicale, malgré les preuves scientifiques et les arguments éthiques contraires.

**Mots-clés**
expérimentation animale, recherche médicale, argument, oncologie, radiobiologie, éthique

**Abstract**
Despite the international 3Rs principles that recommends replacing, reducing and refining the use of animals in medical experimentation, it remains difficult to obtain funding in Canada for medical research that respects these principles, particularly with regard to replacement. This observation led our team to review the literature on the arguments for and against animal experimentation in the fields of oncology and radiobiology. This article presents a synthesis of these arguments. Using the method created by McCullough and colleagues to conduct critical reviews of the ethics literature, we analysed 25 texts discussing the arguments for and against animal experimentation in oncology and radiobiology. Six broad categories of arguments for animal experimentation and eleven categories of arguments against it emerged from our analyses. Furthermore, the arguments against animal testing are more convincing from both an empirical and normative perspective. Also, most arguments obtained are transferable in other fields of medicine. In addition to the literature review, a critical reflection was conducted and other arguments were discussed. It seems that a conservative culture persists in medical research, despite the scientific evidence and ethical arguments to the contrary.

**Keywords**
animal experiment, medical research, argument, oncology, radiobiology, ethics

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## INTRODUCTION

Animal[1] experimentation has a long history of practice and is even mentioned in ancient writings such as those of Aristotle and Erasistratus (1). In its systematic form, animal experimentation has been conceptualized as part of the development of the scientific method, with Francis Bacon (2) first proposing the idea of creating specific places to conduct trials and dissections on animals so that results could then be applied to humans. Claude Bernard (3), the father of vivisection, considered this practice to be essential to the study of physiology and advancement of scientific medicine. And it is with the help of animal testing that the biological sciences have developed to where they are today. This use is no longer just a fact of research, but now a widely held norm for the conduct of ethical research; to not first conduct animal studies is considered, in the collective imagination of much of the scientific community – notably in physiology and medicine – as a grave methodological fault.

Of course, almost since the very beginning of modern science, there has also been resistance on the part of certain groups and individuals with regard to animal experimentation. For example, in the literary domain of the 17th and 18th centuries, several satires opposing this type of experimentation were published (4). The Enlightenment philosopher Voltaire condemned vivisection[2] and the Cartesian myth of the "animal machine", according to which animals could not feel pain (6). O'Meara, a specialist of physiology at the time, protested against the "torture" inflicted on animals, which, according to him, altered the

[1] We use the term "animals" in the text to be brief, but we are talking about non-human animals more specifically.
[2] The term "vivisection", whose first known use dates to 1707, means "the cutting of or operation on a living animal usually for physiological or pathological investigation." (5)


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nature of the bodies being studied and therefore the quality of the eventual results (7). During the 19th century in the United Kingdom, animal protection societies were formed, such as the Society for the Prevention of Cruelty to Animals (SPCA), established in 1824, the Victoria Street Society for the Protection of Animals from Vivisection in 1875, and the British Union for the Abolition of Vivisection in 1898. Further, laws were enacted to counter cruelty in animal experiments, notably with the Cruelty to Animals Act of 1876 (8). These are only but a few examples of instances where people in past centuries have stood against the use of vivisection and animal testing.

The number of animals used in research has increased enormously over the years. In 2005, it was estimated that more than 115 million animals worldwide were used for research (9), figures that were described by Knight as conservative (10), who estimated the number to be at least 127 million. Concurrently with this increase, large numbers of animal rights advocates have been lobbying against animal use in research. For example, in the United States there was an increase in the number of anti-animal cruelty organizations between 1967 and 2000, from about 1,000 to over 7,000, with membership growing from a few million to over 10 million (11). The global organization People for the Ethical Treatment of Animals (PETA) had 350,000 members in 1990 (12), but by 2020 their membership had expanded to more than 6.5 million (13). The philosophers who were probably the most influential in contributing to this increased public sensibility are Peter Singer and his book *Animal Liberation* (14), which develops arguments on the basis of animal welfare, and Tom Regan with his book *The Case for Animal Rights* (15) which, for its part, defends the rights of animals. It is thus fair to say that public concern about animal experimentation has been a topic of signficant debate for decades, with it's origins in 18th and 19th centuries.

The 3Rs – which stand for *Replacement* of animals by other means, *Reduction* of the number of animals used to obtain information and *Refinement* of the methods used to minimize suffering – are three principles first proposed over 60 years ago (16). Now widely adopted by the scientific community and by many governments, these principles have been guiding laboratory research done on animals since the 1990s (16-18). Despite broad agreement on the 3Rs, animal experimentation is still the default method for much scientific (and especially clinical) research. Even if not always required, the majority of studies in medicine, for example, continue to use animal experiments to assess the risks and relevant results before proceeding to human studies (20). Furthermore, it can be very difficult to obtain grants from funding agencies when researchers wish to proceed withou recourse to animal experimentation. For example, in trying to obtain funding to support a project to treat radio-dermatitis caused by radiation therapy to treat cancer, our project – which respected the 3Rs principles – was criticized for not first doing animal studies. These comments led us to question an apparent culture in Canadian medical research that seems closed to the 3Rs principles (19).

In our grant application, we had provided arguments to justify compliance with the 3Rs principles, notably the replacement of animals with tissues made in laboratory from human cells. On the one hand, some of our arguments reflected the general problem of animal experimentation. For instance, because of the important differences between animals and human beings, only a small proportion of animal experiments lead to satisfactory results in order to move forward with a clinical phase, which is a major transferability problem (20-22). Moreover, there is a direct violation of animal rights and welfare in the use of animals in research (14,23,24). Thus, there is a need for methodological change in order to decrease or even avoid animal experimentation, where possible, as in many cases it is unnecessary (20-22). On the other hand, our other arguments were related to the methodological innovation inherent to the project due to its absence of animal experiments. Since animals do not have the same physiology of cancer-related neoplastic tissues as do humans (25), conducting our experiment on animals did not seem justified because the results would not be representative of a need in humans, and this would cause unjustified delays and needless animal suffering. In addition, there do not appear to be any systematic reviews about the usefulness of animal studies and radiation damage in the context of radiotherapy research (26). Thus, in our project, the use of living human skins as an alternative to animal experimentation was justified since it would have allowed us to establish a more direct correlation with the affect of radiation on humans (27-29), increasing the relevance of the results, and so would probably have contributed to human well-being in a better time frame than if we had first proceeded with animal experimentation.

In short, as is often the case in the history of ideas, there is a gap between the internationally advocated 3Rs principles and the way medical science is actually conducted, at least in Canada. More specifically, it is a priori the replacement of animal studies that seems to pose the most problem. This observation and our experience of being confronted with a status quo view on animal experimentation led us to conduct a critical and comprehensive review of writings arguing for the ethical justifiability of animal experimentation in oncology and radiological biology. The general question underlying our critical review was the following: *What are the arguments for and against animal experimentation in oncology and radiological biology?* But as we will see, the answers to our initial question go beyond oncology and radiological biology. In fact, they broaden the target audience to include not only researchers and practitioners in these fields of research, but also the entire scientific community, since the arguments raised concern society in general. So one of the contribution of this article is that it provides readers who are already familiar with the arguments for and against animal experimentation with a systematic understanding of the state of the literature, although perhaps not exhaustive due to the initial question which limited the number of results considerably.

## RESEARCH METHODS

In order to answer our general question, we conducted a critical literature review, using the McCullough, Coverdale and Chervenak methodology (30,31), to examine how ethical and scientific issues encountered in animal research in the fields of oncology and radiological biology are discussed in the academic literature. We selected this approach because it is one of the methods recommended for conducting a comprehensive and critical review and because we have used it successfully on

several occasions to conduct literature reviews on ethical concepts (32-34). That said, we adapted the method to specifically identify the elements of interest that we were seeking in this review, namely the arguments for and against animal experimentation, thus joining the suggestions of other authors in the field of bioethics for conducting such reviews (35,36). Also, it was the experiential knowledge of some of the authors of this article in relation to the conservatism of the last few decades in animal experimentation that led us to undertake this research. This method involves four steps in order to identify and critically evaluate the ethical arguments appearing in the literature: 1) identify research questions relevant to our process; 2) conduct a literature search using key terms relevant to the research questions; 3) extract and synthesize data from selected literature in order to answer the research questions; 4) critically assess the scope of the ethical and scientific arguments put forward.

## Step 1: Identify research questions relevant to our process

Two research questions have been selected in order to guide our critical review and provide answers to the general question at the origin of this study: a) What are the arguments in favour of animal experimentation and what could justify the refusal of alternatives to animal testing in oncology and radiobiology, i.e., methods respecting the 3Rs principles? b) What are the arguments against animal experimentation and what could justify the use of alternatives to animal testing in oncology and radiobiology?

## Step 2: Conduct a literature search using key terms pertinent to the research questions

In order to answer the research questions, we have conducted a literature search by consulting six databases chosen based on their relevance in fields of ethics, namely: Academic Search Complete, CINAHL, JSTOR, Philosopher's Index, ProQuest, and Scopus. The literature review was conducted from October 2019 to March 2020. Four categories of keywords were combined in various ways, mostly by using no more than one word from the same category at a time (see Table 1); more specifically, we used "and" between categories and "or" within a category.

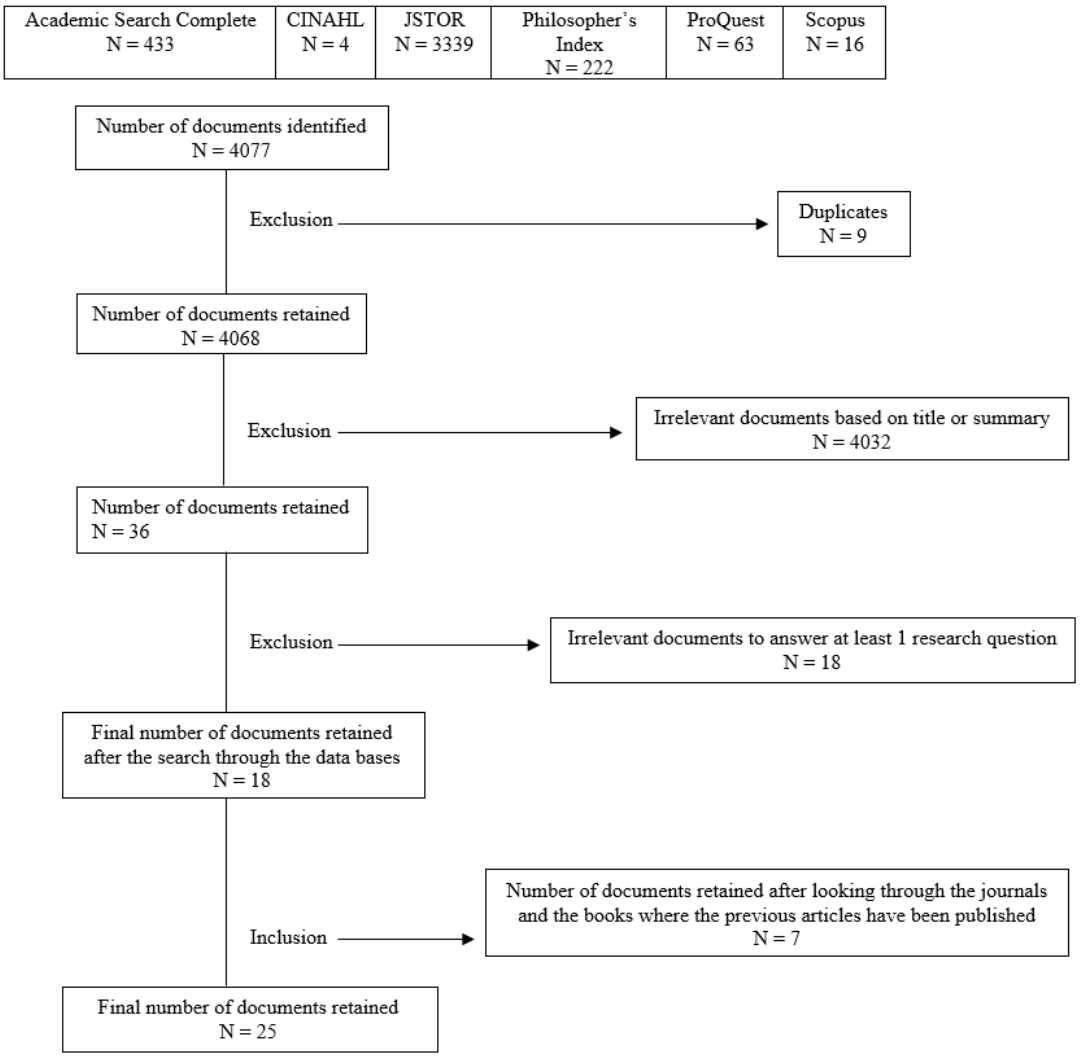
**Table 1: Keywords used to identify relevant literature**

| Words related to 'ethics' and 'argument' | Words related to 'animal experimentation' | Words related to 'cancer' | Words related to 'alternatives' |
|---|---|---|---|
| ethic*<br>3Rs*<br>moral*<br>rational*<br>argument*<br>reason* | research*<br>animal<br>experimentation*<br>science*<br>animal research*<br>animal testing* | radiobiology*<br>oncolog*<br>radiation*<br>cancer*<br>breast<br>cancer*<br>neck cancer* | Alternative method*<br>alternative*<br>ex vivo*<br>human tissue*<br>in vitro*<br>skin* |

Support from the authors' university library, i.e., at the Université du Québec à Trois-Rivières (UQTR), made possible the use of open and restricted access databases. All databases were chosen because of their accessibility and because they could present relevant documentation. In order to be included, a document had to be written in languages understood by the authors (English and French), to answer at least one of the research questions and to be free to access through the UQTR library system. We did not exclude articles based on publication date since we wanted to obtain as much literature as possible on the arguments in favour and against animal experimentation or its alternatives in both fields of oncology and radiobiology. The dataset included peer-reviewed articles and book chapters. In addition to sources proposed by McCullough, Coverdale and Chervenak's method, we also included some articles that were not necessarily peer-reviewed (gray literature) for their relevance. Finally, we added book chapters or articles that were not found through the databases but were proposed by reviewers or found alongside identified texts, e.g., in their respective journals or books. Those sources found in a manner other than the method proposed by McCullough, Coverdale and Chervenak are identified by an asterisk (*).

Figure 1 presents the choices that were made to exclude some documents due to their irrelevance, and an overview of the main steps that led to the ethical analysis of the results. In the end, we reviewed 25 documents that met all of the above-mentioned inclusion criteria. We first extracted information in order to describe the corpus of documents. We identified the discipline, the type of document, the date of publication and the country of origin of both researchers and publishers.

**Figure 1: Main steps of the literature review**




In September 2021, we conducted a second search using PubMed to add articles from which we could extract arguments for and against animal experimentation in oncology and radiological biology. Thousands of results emerged using the same method as in our first search. However, since we were already advanced in the analysis, we limited the search to a single keyword combination that yielded 15 potential articles: ((ethical) OR (moral*) OR (argument)) AND ((animal experimentation) OR (animal experimentation*) OR (animal research*) OR (animal testing*)) AND ((radiobiology*) OR (radiological ontology*)) AND ((alternatives) OR (alternative method*) OR (alternative) OR (ex vivo*) OR (human tissue*) OR (in vitro*) OR (skin*)). Of these 15 articles, only 3 were retained for data extraction. A more exhaustive search on PubMed could lead to the extraction of arguments from a larger number of papers. Considering the time interval between the first and second search, we decided not to integrate in the results the arguments found in the second search, and so we present these in a separate section at the end of the results section. No new argument categories emerged from this second search and we associated the already existing categories with each argument found in the three targeted articles.

## Step 3: Extract and synthesize data from the selected literature to answer the research questions

A data extraction table was designed to extract the sought-after answers to our research questions. Then, we synthesized the information to portray a general view of arguments about the use of animal experimentation and its alternatives. While doing this, we categorized specific arguments into general categories which were generated inductively on the basis of an analysis of the arguments present in the literature. The overview of those arguments is further developed in the Results section.

## Step 4: Critically assess the scope of the ethical and scientific arguments put forward

Following the selection of the arguments proposed by the authors in the article sample set, we subjected these to critical reflection to evaluate whether or not animal experimentation in the fields of oncology and radiological biology was considered desirable or not and whether alternatives to it were preferable. Our reflection is further developed in the Discussion section.

## RESULTS OF THE CRITICAL LITERATURE REVIEW

After describing the corpus of documents found through our database searches, the arguments for and against animal experimentation in oncology and radiological biology are presented. The discussion of these results follows in the next section.

### Description of the corpus

The chosen texts were published between 1997 and 2019. As seen on Figure 2, there has been an increase in number of publications starting from 2012. The years with the most publications were 2015 with 24% of the documents published and 2019 with 32%. Within the 25 texts, 15 were from peer-reviewed journals (60%), 8 were chapters from the same book (32%) and 2 were from gray literature (8%). All documents were written in English.

**Figure 2: Number of texts by year of publication**

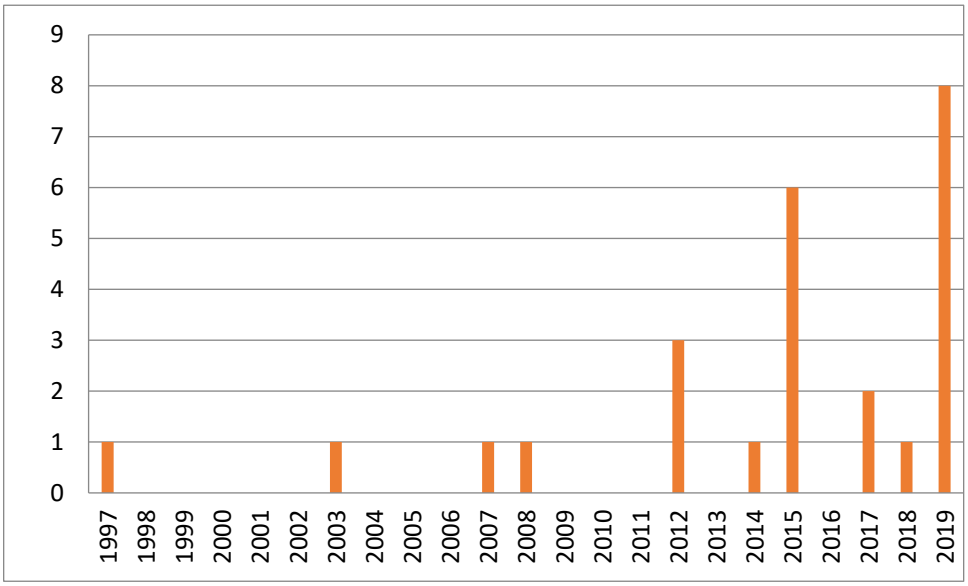
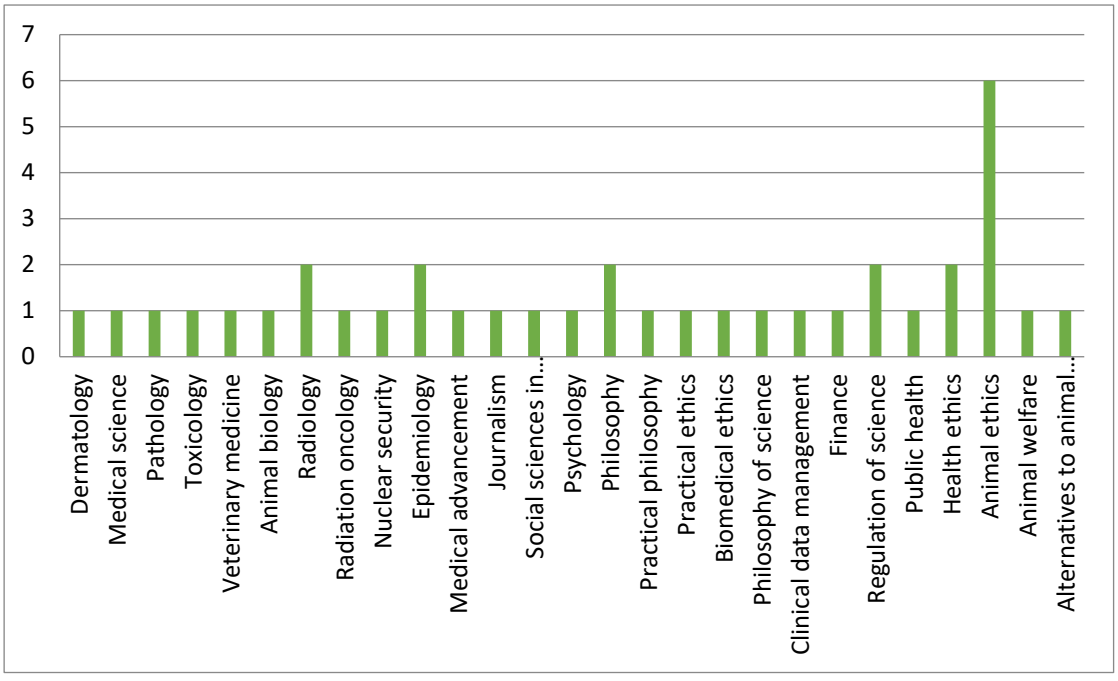


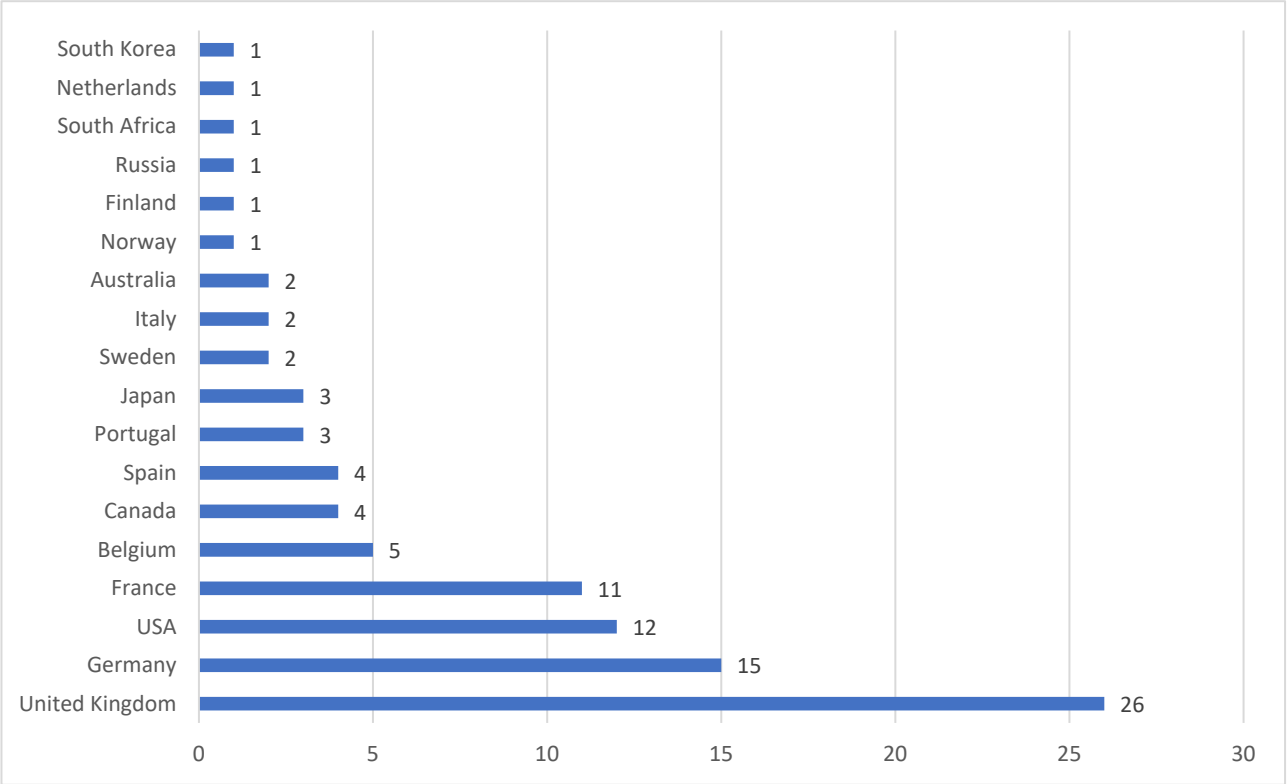

Figure 3 shows the number of texts where the fields of work are represented by at least 1 author; this was determined by taking into account the affiliation of the main author of the articles. It is notable that for 24% of the texts (n = 6) there is at least 1 author from the field of animal ethics.

**Figure 3: Number of texts where the fields of work are represented by at least 1 author**



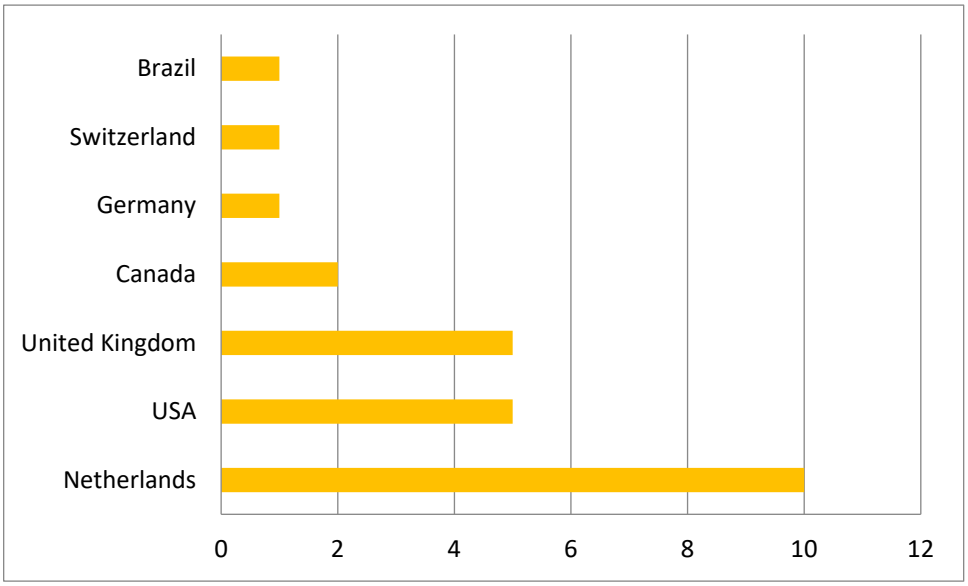
Among the 95 authors who contributed to the various texts, 40% (n = 38) were from the United States (n = 12) and from the United Kingdom (n = 26), although German authors (n = 15) slightly exceeded Americans (see Figure 4).

**Figure 4: Number of authors by country**




In addition, as shown in Figure 5, 40% of the texts were published by journals or editors located in the Netherlands (n = 10), 20% in the United Kingdom (n = 5), and 20% in the United States (n = 5). Altogether, texts published in the United States and in the United Kingdom represent 40% of the countries of publishers.

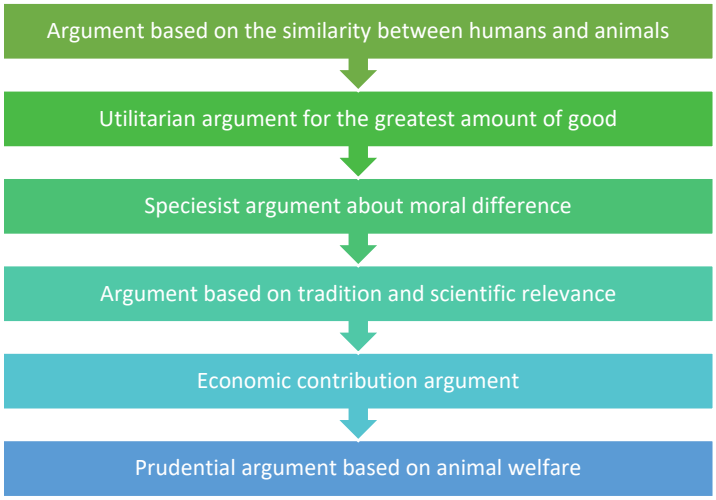
**Figure 5: Number of writings by country of publishers**



## Arguments for animal experimentation

What are the arguments in favour of animal experimentation and what could justify the refusal of alternatives to animal testing in oncology and radiobiology? As Figure 6 illustrates, six broad categories of arguments emerge from the literature review. These are summarized in the following paragraphs.

**Figure 6: Categories of argument in favour of animal experimentation**




### *Argument based on the similarity between humans and animals*

It is argued that the use of animals in research is justifiable because they form complex living systems similar to those of humans and are therefore suitable as models for more complex comprehension of responses at the level of the whole organism (37). *In vivo* methods take better account than *in vitro* methods of the biological complexity of each tissue in interaction with other tissues (38,39). Thus, the use of alternatives can, for instance, cause the loss of complete immune responses present in animals (40) or possible reactions of a molecule (41). In addition, the lack of human data sometimes limits the predictions of *in silico* models because they may not adequately predict responses to a new disease (37).

### *Utilitarian argument for the greatest amount of good*

In contemporary society, it seems appropriate to use animal testing whenever it achieves benefits for human or animal health and the environment (42,43). These benefits are greater than the negative impacts on millions of laboratory animals (44-46) or on humans (47). Animal research offers unique benefits to humans that could not be achieved without it, and among other things, it avoids risks to human health while contribution to the generation of new knowledge (47,48).

### *Speciesist argument about moral difference*

First and foremost, some state that we have a moral obligation towards human beings (49) because human beings are people (unlike animals) (45,47,49), because they have cognitive abilities and self-awareness (43,45,46), because human beings are capable of demanding rights for themselves (45), and finally, because they are part of a certain “kind” that distinguishes them from animals and that allows them to be part of the human moral community even if they lost their physical or mental capacities (43,46). In fact, some authors even claim that animals have no moral status at all (47). Only humans determine which animals they come into contact with (49) and can show partiality in the same way as they are partial with their family or friends (43).

### *Argument based on tradition and scientific relevance*

Animal testing has been used for decades in research and development of new medicines (50,51) and changing people’s habits may be difficult for them to accept (51). As proclaimed by some authors, “the greatest successes of medicine are due to animal experimentation”, which is therefore essential (48), effective (49) and gives the impression of being more efficient (44) and less risky (52,53) than using alternatives. We must consider the body of biomedical knowledge accumulated up to now due to animal experimentation as well as our accumulated knowledge on different human diseases (54).

With the guidelines now available to researchers, there may be fewer methodological flaws and redundancy in studies using animals (37,53), which will, among other things, allow better reproducibility (52) and maximize the usefulness of published studies (53). Moreover, some believe that animal testing is necessary because there are no real alternatives (43). The alternatives to animal testing have yet to prove that they can be as effective as the established methods (53) or that they will always be an improvement compared to animal testing (39,41), which should in principle be done by continuing to use the “tried and true” methods to compare with the new “unproven” methods (53).

The methods of collecting and storing tissue samples, as well as confounding factors such as age or lifestyle, may affect the usefulness of the tissue collected in certain analyses, such as studies conducted following ionizing radiation (38). Similarly, there is uncertainty regarding the effects of time between the moment of *ex vivo* radiation and the collection of biological samples for research (55). In addition, access to biological samples under optimal conditions of collection and storage is

quantitatively limited for reasons related to the time for obtaining and analysing the results (which may limit their use in studies large scale), among others (38). Due to the low rate of collected and stored biological samples used in studies, the statistical power is low (38,39).

### *Economic contribution argument*

Abolishing animal testing could eliminate certain tasks or even jobs and harm the personal goals that people set for themselves, while depriving institutions from receiving funds that allow them to cover administrative costs (51). Because the use of animals in research is less ethically demanding than it is for research with humans, access to animals is faster and cost effective (37). Validation processes for the quality of alternatives to animal testing cost money and time (53). In addition, the data produced by the alternative methods can be very complex for interpretation and therefore may require some expertise which was unnecessary with traditional methods (53).

### *Prudential argument based on animal welfare*

Animal research must be careful, that is, it must be able to make good decisions despite the uncertainties (56). Animal testing should be allowed and is morally justifiable when it is similar to research conducted on humans and with the same sensitivity, because huge benefits emerge (43) and no unnecessary harm is done to animals (necessity determined by the purpose of the research) (47). Animal experimentation is morally justifiable if the life of the animal is worth living despite the experiments that are carried out: the interests of the animal are then taken into account and the benefits could be greater in comparison to the harms (47). It seems immoral to bring beings into life and then make their lives miserable, and certain relationships lead people in position of authority to protect those who depend on them and who are vulnerable, as is the case for animals (47). Failure to comply with just one of the conditions of net benefit, life worth living or no unnecessary harm means that an experiment is no longer morally permissible, regardless of whether the other conditions are met; thus a researcher cannot morally justify their research on the basis of a single necessary condition (47).

## Arguments against animal experimentation

What are the arguments against animal experimentation and what could justify alternatives to animal testing in oncology and radiobiology? As Figure 7 illustrates, eleven broad categories of arguments emerge from the literature review. These are summarized in the following paragraphs.

**Figure 7: Categories of arguments against animal experimentation**

### *Argument for the so-called utility of animal experimentation*

The calculation of benefits versus harm goes against animal testing since everything suggests that the benefits to humans from this practice are too low to outweigh the harms caused to both animals and humans (43,48,54). Authors note that there are only a few anecdotes concerning the major cases of animal research that have worked (47), and these do not constitute a systematic justification of favourable results (46). Some think that all harms caused to humans by experimenting on animals should be part of the calculation of benefits versus harms (46), including counterfactual harms and benefits, i.e., those that could have happened if there had been less or more animal testing (47). Research on radiation exposure that does more harm than good should not take place according to the principle of justification, which is a principle of exposure that applies to the different types of situations and categories of exposure (56). In general, according to Galgut (46), human interests are overrated when it comes to defending animal experimentation: animal experiments are often conducted with the aim of relieving superficial conditions related to comfort rather than suffering or potentially fatal conditions. This should then reduce the weight given to the benefits of animal testing compared to the harm caused to animals (46). Much of animal testing is used in basic research, which by definition does not necessarily lead to applications for humans (46). As such, the benefits for humans of basic research are largely unknown, making impossible the utilitarian justification that animal experimentation in basic research can benefit human beings more than causing harm to animals (46). Advocates of animal testing must also demonstrate the need for its use and why alternatives would not have worked to achieve the same results (46,57). Given the present alternatives to animal testing that did not previously exist, the benefits of animal testing that may have seemed unique do not guarantee sigificant future benefits (47). It is important to note that harm-benefit analyses are done prospectively, before the experiments are conducted*. What is needed in order to demonstrate that harms in most cases outweigh benefits is to make retrospective harm-benefit-analyses more frequent and even obligatory*. In the EU, the experimenter needs to assess and report the actual severity of procedures on an individual animal (17*).

### *Argument about the false similarity between animal and human models, and possible alternatives*

Several limitations inherent in species differences are likely impossible to overcome, such as fundamental biochemical differences that can alter the way organs react and the magnitude of these differences (44,52,58). Also, the variability of human populations is not necessarily captured by animal models (53), nor is the complexity of human disease when it is reproduced in animals (59). Furthermore, the biological complexity of each species can lead to different results within the same experimental manipulations (37,50-54,57-60). Likewise, subjective symptoms are rarely objectifiable as are behaviours, therefore making it difficult for researchers to establish a clear link between the two models for a given phenomenon (49). Caution with regards to extrapolating the results from animals to humans with full knowledge of the differences is insufficient since it is doubtful that we can accurately select all the relevant differences and then determine what is or is not applicable to humans (59). It follows that humans are the best biomedical model for humans (37,52).

Alternatives to animal experimentation sometimes make it possible to better understand certain complex mechanisms (53) and to experiment with better quality and better reliability since they take better account of the complexity of human biological systems (40,48,52,59) in comparison with the body of the animal which sometimes acts as a black box (40). According to some, we should still use more than one alternative to an animal experiment in order to accurately estimate certain mechanisms, as several factors may come into play in the process studied (40). Some authors also believe that we should modify our ethical values so that more risk is sometimes placed on human shoulders by not using animals for experiments (41).

*In vitro* experimentation reveals the mechanisms of action more clearly (40) as well as “off-target” effects that depend on the species and which cannot be discovered by animal experimentation (52). This approach gets around the metabolic barrier between the different species since the tests are done directly on human cells, which should thereby increase predictability (39). *Ex vivo* methods are useful when repeated sampling before and during irradiation is not possible, and in retrospective studies where it is not possible to measure biological responses that occurred many years ago (55). Pernot et al. (38) consider that in the case of exposure to radiation, the *in vitro* method is useful for predicting individual susceptibility to radiation, and it provides greater precision since the doses of radiation can be controlled more strictly, and time-related responses are more easily measured. *In silico* techniques can fill the need for researchers to have complete complex living models by simulating these models from humans themselves (37,59). In addition to using animal-free, human-relevant methods, clinical, epidemiological and biomonitoring data can be used. These data have been historically underused in research and could help replace the unnecessary use of animals while improving research results and patient safety (50).

### *Animal welfare argument*

Animal research is detrimental to the animals’ interests as it harms the maintenance of their lives and the integrity of their bodies and minds (43-45,54,57). Animal experimentation causes significant sources of fear and distress as well as pain and suffering in laboratory animals – e.g., by capturing wild animals, transportation, conditions of habitation in laboratories, invasive or routine procedures, etc. (44,46,48,60) – that, with the physiological changes undergone, can alter the results of studies (48,59,60,61*). Some animals may not receive research anesthesia and analgesia in rare cases where it would affect outcomes, which is a serious infringement on their welfare (48). The loss of pleasures is also a harm caused to research animals, since they do not have access to all the pleasures they would be allowed to have if they had lived in another context: we would not accept that only basic human needs should be met (46). The death of animals at the end of several experiments is as wrong for these animals as it would be for humans since it prevents them from pursuing their interests (46). This situation could be mitigated by providing these animals with the necessary care and a peaceful retirement (46). In the meantime, according to Cojocaru and von Gall (42), the fact that the objectifying language of animal experimentation considers in their

classification the killing of animals to be the least serious form of suffering shows that it does not appropriately understand animal suffering.

Studies using low doses of exposure to ionizing radiation show that this increases the risk of developing cancer, and at higher doses, of developing heart disease or cataracts in the animals on which these experiments were performed (55). However, principles of beneficence and non-maleficence must take into account the impact of radiation on health (56). According to the principles of optimization and limitation of individual doses, exposure to radiation should be held as low as reasonably achievable and should not exceed the limits recommended by the International Commission on Radiological Protection (ICRP) (56).

The ethical consideration of respect for life should encourage the elimination of animal suffering (62). There is no reason to think that the life experience of the animal is worth less than the one of the human being and that it deserves less moral weight, because we do not have access to their subjective experiences nor to the sense that these experiences can have for them (45). Likewise, it is inequitable to expose only a few individuals to radiation; all individuals are entitled to the same treatment and should receive the same consideration of their opinions if they are involved in radiation protection (56). Alternatives to animal testing help avoid or minimize animal pain and suffering (40,41), which is in accordance with the 3Rs principles (50,62).

### *Argument for the ethical status of animals*

According to many scholars, animals should be protected because of their ability to sense (45,47,49,62) and their awareness (62), which sometimes allows them to be described as persons who should have the same rights as humans (45,49). Some authors believe that the argument of the fundamental difference between human and animal on a moral level is questionable since it is not really reflected in many of our actions; for example, we do not decide if a human person has the right to live on the basis that they can deliberate and act on moral principles (43). Also, the characteristics raised to justify this argument are not morally relevant to the extent that they are often not present in certain human beings and can be more present in certain animals (43,46). Speciesism cannot justify the use of animals even if alternatives did not exist (51). Simply belonging to the human species (46) or to human kind (43) does not succeed in morally justifying treating differently animals and human beings. Nor does the argument that one should be partial to a human being as one would be to a family member justify a negative difference in treatment, since this argument only says that one can benefit some and not harm others (43). Likewise, rights are logically correlative to obligations and our moral obligation towards animals justify the view that they have moral rights, regardless of their ability to claim them, as in humans who do not have to claim rights for themselves in order to have them (45). Since it does not take into account the consent of animals, animal experimentation would be considered unethical if it was carried out on human beings (43,57); animal-free methods should thus be used since the animal is a *subject of a life* (11) that has rights (49). Our moral intuitions lead us to believe that the most vulnerable people are those who need the most moral protection; animals are just as vulnerable, and they also deserve increased moral protection (45,46). On the one hand, animals are objectified in research, and they are treated as mere means rather than as ends in themselves (47,60). On the other hand, as recognized by UNESCO's Universal Declaration of Animal Rights, animals must be protected (62).

### *Argument stemming from tradition and easiness*

Studies using animal testing are often conducted only because it is what is asked for and not because the data collected is useful (41,52,53); studies conducted without animal testing thus have to combat a "procedural fossilization" (41). The use of animal models in research has become the scientific gold standard against which other models are compared because there has been an appearance that this model has worked well in the past; however, whether the model works or not, there are appeals to tradition that push us to be psychologically motivated to continue to use animals in research, even if the use is unjustified (46,50) and the necessity has yet to be proven (50). In fact, the value of current methods of animal experimentation has never been formally proven (39,49,50,52) since the validity tests of the methods are very long and expensive (52), and that the new data must usually be compared with those coming from experiments conducted on animals (50,52). Despite the ethical implications of choosing species for animal testing, these choices are often made based on accessibility rather than relevance to the experiment (49).

### *Economic argument*

According to Hansen and Kosberg (54), the low human benefits are not worth the public money spent on animal studies. The argument of the defenders of animal experimentation, according to which they have as an objective to reduce mortality, does not work because if one invested the money elsewhere, e.g., to finance hygiene measures in poor countries, we would save more human lives (54). Animal-free, human-biology based models and methods can meet the pragmatic needs of researchers, since they save time because animal testing requires going through many stages before being approved (39-41,47,53,51-53,60), and they would even potentially save money because such experimentation is expensive (39-41,47,48,51-53,60). Unlike in animal experimentation, there is a return on investment compared to the effects on patient care when alternatives to animal testing are used (47,50,53).

### *Argument about the impediment to progress*

Animal research is perceived by some as an issue where the scientific community has dogmatically refused progress by continuing to use outdated techniques despite knowledge of their limitations (50) and despite the smaller potential for development (44). The appeal to the tradition of animal testing prevents change from occuring because even when space is given by regulators to non-animal, human-relevant methods, the results must often still be confirmed by experiments carried out on animals (50). As much human research data as possible is needed to enable future complete simulation models (i.e.,

computer models) (40) – and if the effort and resourced devoted to animal experimentation were instead directed to the development of non-animal methods, there could be major advances in this area (41,59). With the example of cosmetics in the European Union, we see that the ban on animal testing has enabled remarkabe advances in the development of alternatives in this domaine (50). Allowing animal-free experiments, if their use is well justified in the case of human safety tests, is also a way of evaluating these new ways of gathering scientific evidence (52).

### *Argument about harms to various human actors involved in animal research*

Researchers or committee members who show too much empathy for animals and who are opposed to animal use in science are victims of a form of alienation that resembles epistemic injustice: the emotions they express are deemed to be unprofessional or irrational and their discourse is rejected (42). As Fricker (63*) points out, epistemic justice is a form of justice that has to do with knowledge, which she distinguishes between two types: *testimonial injustice* is related to the fact that people's words are unfairly devalued, while *hermeneutic injustice* refers to the fact that people are confronted with the absence of epistemic resources that would allow them to describe what they experience. The issue described by Cojocaru and von Gall is thus similar to an epistemic injustice of a testimonial nature. It leads to polarized opinions and only a partial understanding of what can be considered acceptable or not (42). Similar to what soldiers and medical personnel experience, researchers involved in animal experiments risk being "morally injured" because of the opposition that there may be between the values of the institution and their own (60). This risk of moral injury to researchers may also be caused by the shift in the moral context between their life as a researcher and their civil life in which they may be ashamed, feel excluded or keep the nature of their work secret for fear of judgment (60).

By objectifying animals in research, the researchers see their own capacity as moral agents to make decisions decreased as their relationship with the animals is not decided by themselves, but by external factors and by institutions (60). Their ability to relate to the outside world is also decreased because they are required to replace their empathetic bond with what surrounds them by a non-influenceable neutrality, which devalues their subjectivity and that of animals and their interests. Ultimately, the autonomy in action of researchers is also decreased since their social sphere is reduced (60).

Animal research workers may experience negative feelings (made worse by the culture of secrecy) and impacts on their physical health because of their involvement in animal harm or because they have witnessed the suffering felt by animals, impacts which can be even greater on laboratory technicians who take care of those animals and who have often chosen their profession because they care about animal welfare (60). Animal experimenters have to desensitize themselves (to passivity in order to dissociate themselves from their actions) if they want to develop within their field, and they experience a certain cognitive dissonance, i.e., tension due to contradictions between their beliefs and their actions, if they cannot do so (60).

### *Transferability argument*

Most systematic reviews conclude that animal experiments are ineffective (especially with regard to cancer and toxicity studies), both in terms of their transferability to clinical outcomes and their safety (37,44,46-48,51,52,54,57,59). For example, Hansen and Kosberg (54), Joffe (57) and Greek and Kramer (51) all cite an article from Contopoulos-Ioannidis et al. (64*) that shows that among 101 articles selected for their claim for future clinical application – drawn from 25,190 articles published in 6 basic science research journals between 1979 and 1983 – only 1 has shown significative results for clinical application. Furthermore, Archibald et al. (52) quote an article from Hutchinson and Kirk (65) which stated that 96% of new cancer treatments fail in clinical trials. Citation analyses tend to show that research using animals is rarely cited in research conducted on humans, and that it is cited largely in other studies that use animals and secondarily since these are mostly non-essential quotes that do not necessarily relate to the disorders described in the articles citing them (37). Because of the imprecision of animal research, several drugs have been proven dangerous for human beings and have not or could not have been marketed if they had been limited to animal testing (47,52,57,59,60). By being non-predictive, research models based on animal experimentation potentially cause many side effects and deaths in the human population, which can cause enormous costs for health systems (46,52). The majority of drugs that are clinically tested do not reach the market because they contain toxicities that were not observed previously in animals or because they lack the predicted therapeutic effects; many of the approved drugs are being withdrawn from the market because they are later deemed unsafe (52).

### *Argument about the limitations of the scientific community*

The use of animals in science is anchored in a belief system that works more for itself than for humans because of its ignorance of human mechanisms. In this system, it is better not to publish the results of animal experiments because failure is frowned upon; and it is better to say that more research needs to be done rather than admitting that something has not worked as expected (50). There is no real scrutiny of the harm caused by animal testing versus their benefits by the committee members who decide on a project's acceptability, as almost all experiments involving animals are accepted by the members of these committees whose judgment is biased by their own interests (54). A large number of recent studies show that research using animals contain a large majority of methodological flaws (with the use of randomization and blinding or details omitted such as the strain of the animal, sex, age, weight, the size of the sample as well as its justification, etc.) which can alter the results of the research (37,48,50,52,54,60). These methodological flaws can become sources of bias that can alter conclusions about the risks and benefits of the drugs presented (52). In addition, animal experiments are sometimes used in conjunction with clinical trials on humans, which shows that their use is not always necessary (37,50). With duplicative experiments, several scientific procedures performed on animals do not even need to be replaced but can simply be eliminated because of their redundancy or because they are simply useless and outdated (50,53). Despite efforts to make research using animals more methodologically comprehensive, research continues using unsatisfactory methods, and many studies ignore the guidelines available to them (48).

#### *Political argument of epistemic justice by giving a voice to democracy*

People generally agree to eliminate the use of certain animals for research and to minimize animal suffering (54) – public opinion supports animal research because people believe it works (51). If the public knew that animal models in drug and disease research had little to no predictive value, people would probably demand its abolition (51). The principle of clinical equipoise, which states that there should be a state of balanced disagreement about the merits of a treatment among the experts of the research field at the start of the clinical treatment, also requires that society be involved in the acceptance of research (66). As Ferrari proposes (67*), the justification of the harm done to animals requires not only an empirical critique, but also a political critique, since the acceptability of science's experiments is a product of social values. In sum, this political argument is based on the value of epistemic justice, in that it is because the public is kept in some form of ignorance that it does not oppose animal experimentation more clearly. Democratic life would be improved by a better sharing of knowledge about the true empirical utility of animal experimentation.

### Arguments for and against animal experimentation from the second literature search

#### *Arguments for animal experimentation*

The porcine model is similar to the human model in some aspects related to irradiation, such as phylogeny, immune system and immune response (argument of the similarity between humans and animals) (68). The results of the *in vitro* model cannot be extrapolated to the *in vivo* model with respect to the absolute leukocyte population, because of scavenging mechanisms and resident leukocytes only present in the *in vivo* model (argument about tradition and scientific relevance) (68).

#### *Arguments against animal experimentation*

*In vitro* models are, in cases of radiotoxicity, able to mimic under controlled conditions human biological systems, such as the human airway epithelium (argument about the false similarity between animal and human models, and possible alternatives) (69). *In vivo* experiments on an organism's responses are resource and animal intensive (economic argument) (69). We can use public archives of animal experiments to limit the overuse of animal experiments (argument about the false similarity between animal and human models, and possible alternatives) (70). Many results of lifespan studies on exposure to different types of radiation are available in public archives of research results. We can use these results to limit the unnecessary use of animals in new studies, for example by comparing with analysis of high-definition histology images of necropsy findings (argument about the false similarity between animal and human models, and possible alternatives) (70). Unused tissue samples could be shared to limit animal use and to create collaborations between institutions (argument about the false similarity between animal and human models, and possible alternatives) (70).

## DISCUSSION OF RESULTS: AN ETHICAL AND CRITICAL REFLECTION

The general question underlying this literature review was the following: *What are the arguments for and against animal experimentation in oncology and radiological biology?* Two specific questions arose from this general questioning, namely: a) What are the arguments in favour of animal experimentation and what could justify the refusal of alternatives to animal testing in oncology and radiobiology? b) What are the arguments against animal experimentation and what could justify the use of alternatives to animal testing in oncology and radiobiology? The previous section reveals that several arguments (six for animal experiment and eleven against) have been identified in the body of texts under review. The following discussion provides a critical reflection on these arguments and adds new arguments not found in the literature examined, before presenting the limitations and strengths of the study.

### Critical analysis of the arguments for and against animal experimentation

All things considered, are the arguments for or against the most convincing? As mentioned earlier, tradition seemed to be the reason why Canadian granting agency reviewers often disregard the 3Rs principles of animal experimentation (16-18). Faced with our difficulty in convincing reviewers of the scientific and ethical relevance of avoiding animal experimentation in order to save human lives more quickly, given the too great physiological differences between human and nonhuman animal skin, we decided to conduct this critical literature review. We felt that we were right (both scientifically and ethically) to avoid such an unnecessary step (animal experimentation) that would cause animal suffering.

A comparative and critical examination of the arguments for and against animal experimentation revealed that the arguments against such experimentation are more convincing both scientifically and ethically. Indeed, the argument of the resemblance between humans and nonhuman animals proves unconvincing, and all the more so in the field of oncology and radiological biology. The physiological differences between human and animal cancers are so large (20) that the poor results of animal experiments in oncology and radiological biology (57) do not seem to justify the unnecessary suffering to animals and the delays engendered by such preliminary animal studies. This is why we proposed in our research project to experiment with radiation on human skins created in laboratory instead of wasting valuable time and funding collecting unnecessary data from animals. Because animal skins react very differently to radiation than human skin (25,26,71), animal experiments in this area of medicine delay needlessly the production of results that are truly applicable to humans. Moreover, animal research in this area is dangerous, as it leads to erroneous conclusions and thus delays the discovery of solutions that can contribute to human health and well-being. It follows that the argument about the similarity between humans and animals as well as that of the greater amount of goods are in final, all things considered, unconvincing.

But what about the moral difference between humans and animals? While humans and animals are biologically similar, as those who argue for the appropriateness of animal experimentation claim, they are not, however, morally similar, they argue, thus again justifying animal experimentation (43,45-47,49). Some authors in the field of animal ethics or political theory challenge the view that there is an ontological or moral difference between humans and animals, which justifies that we use them for research, eat them or their products, deprive them of their freedom, use them for our own entertainment, and so forth (72-75). Yet, this separation between human and animals is increasingly being challenged by growing number of thinkers. This awareness related to contemporary research shows that animals are sentient beings who experience emotions and sensations, and they are conscious beings in their own way, and in a similar way to humans (76). People, who work in medical laboratories and those who have companion animals experience this on a daily basis: animals experience pleasure and pain as well as a conscience of their own. This supposed moral or ontological schism between human and animals is challenged and invalidated by contemporary scientific developments. Maintaining this radical separation is unfounded and a form of speciesism as Singer (14) argued nearly 50 years ago and continues to defend today (77). Along with science's use of objectifying language about animals (42), we believe that the language that most of us use on a daily basis about them, naming animals on the one hand and humans on the other, as if humans were not animals, is indicative of the still dominant conservative culture. This ethical blindness transcends all cultural organizations, including health granting agencies, at least in the case of those we have worked with in Canada. This language is a reminiscent of this unjustified moral or ontological schism that we often establish between animals and humans. It shows the hegemony of a conservative medical culture that hinders a paradigm change in research towards human biology-based methods.

The economic contribution argument claims that access to animals is faster and cost effective (37). In fact, experiments in animals require many more stages, necessitating more time and money before being approved (39-41,47,48,51-53,60). Since animal experimentation is expensive and may require more time, animal-free alternatives could lead to cost-beneficial research. Even if this may not always be true as new methods can still be very expensive (37,53), we believe that developing these new technologies today could reduce the cost of future development tomorrow.

A point to consider which could partly explain the lack of consideration for animal agency is that they are often perceived as research objects or tools rather than as subjects. There is a voice unheard in animal experimentation, and it is the voice of those who are most involved. Without their consent, we speak for animals and tend to forget the most basic question: if we were in their place, would we want to be treated the same way they are? The problem encountered sounds like what Miranda Fricker (63*) calls epistemic injustice, i.e., an unfair doubt to recognize someone as a producer of knowledge in discourse. Of course, there is some account of animals as sentient beings who can suffer and measures are taken to somewhat protect them. But when we choose what degree of suffering is acceptable to inflict on animals, we overlook the subjective nature of suffering, insofar as the subject who suffers is the only one to feel this suffering and to know if it is acceptable or not. Acknowledging the qualitative part of suffering could be a way to develop researchers' empathy and prevent them from alienation while responding to the need of empathy from those they work with (78). Furthermore, the cognitive dissonance of animal experimentation may be due to the fact that even within scientific procedures where there is manipulation of animals, animal consciousness is naturalized, in the phenomenological sense that it is seen through the objectifying theoretical spectrum of scientific knowledge, rather than what it is when encountered in everyday life. In other words, the subjective construction of meaning by animal life is forgotten and the animal is perceived only through the objective conditions of its environment (79). The naturalization of animal consciousness thus perhaps gives us a technical view of animals as beings that can be used by science as mere resources.

Desensitization to the use of animals for medical experiments (60) might explain much of the tradition argument. Students or young researchers who wish to do research are often opposed to embark on the big (giant!) boat of research where there are animal experiments. So either they get on the big boat by desensitizing themselves, or they try to continue on their own in their canoe for as long as they can, or they let go and no longer do research in areas where animal experimentation is present. If they continue on their own, there is a good chance that they will not be able to obtain research funding, even when justified. It is much more difficult for those who do not want to get on the big boat since the fundable study invariably has to include animal experiments. As such, researchers in the big boat are, for the most part, desensitized and are also the ones who decide who can get on the big boat of research, keeping alive a vicious cycle of a conservative and persistent tradition.

Many place the burden on the animal advocates of proving that animal-free, human-relevant methods are at least as effective as (53) or more effective (39,41) than animal experimentation. But how can the comparison even be possible if there is a refusal to fund research that uses alternatives to animal experimentation? As a response to that unreasonable expectation, the argument of impediment to progress is strong. Indeed, with the case of cosmetics in the European Union, there is a significant empirical evidence that the ban of animal experimentation leads to major development of alternatives (50) and that it could also be the case in other scientific fields like toxicology if more research using non-animal methods were funded (41,59). If science is based on the idea of progress, then both researchers and members of funding agencies (and grant review committees) should focus on the development and use of animal-free, human-relevant methods.

## Other arguments against animal experimentation: Dosimetry and physiological arguments

Other arguments could have reinforced this review if it had been carried out in other fields, in particular in pharmaceutical research. Doses required for drugs in humans are weight-related (80). For animals, not only does the dose change with weight,

but it also changes with species (81). For example, xylazine is used in veterinary anesthesiology for muscle relaxation, sedation and analgesia, where the dose is 1 to 2 mg / kg for a cat, a dog or a horse, but 0.11 to 0.33 mg / kg for cattle (81). A rule of three (cross-multiplication) with dose by weight cannot be used as standard. Also, the dosage varies depending on the route of administration (81). Another example is the anti-inflammatory drug meloxicam: the average oral dose for a 60 kg human is 7.5 mg per day with a maximum of 15 mg, which represents 0.13 to 0.25 mg/kg per day (82), while the dose per day is 0.05 mg/kg for a cat, 0.1 mg/kg for a dog, 0.5 mg/kg for a cow and 1 to 2 mg/kg for a mouse or a rat (81). Also, the physiological response may differ between species. A drug can have: a) no physiological reaction for a species; b) a positive physiological reaction for another species; c) a negative physiological reaction for a third species. It is not only a question of dose; it is also a question of the drug itself. For example, acetaminophen is safely used for humans as a pain killer, but it can be fatal for cats and other animals where, within hours, it prevents the transport of oxygen in the blood by formation of methemoglobin (hemoglobin not functional to carry oxygen) (83,84).

It is thus quite possible that, among all the animal experiments carried out, many gave rise to “no physiological reaction” or “negative physiological reaction” and so were not continued for a human clinical study, even though the physiological reaction of humans could have been positive! This adds to the arguments of transferability and false similarity. Conversely, many studies show an animal physiological reaction to be positive or without effect, whereas in humans gives unsatisfactory results (20-22). An example is the scandal of thalidomide, where no toxicity was found in several generation of rabbits, mice, hamsters and chickens, but in humans caused severe birth defects, excessive thrombosis, increased anemia, etc. (85).

### Limitations and strengths of the critical literature review

This review has some limitations, notably the heterogeneity of included studies and the field of work, and that most studies were conducted after 2015. Moreover, the small numbers of included papers add to the limitations of this review, whether it is with the first search or for the short second search through PubMed. As such, further and more extensive literature searches need to be conducted, whether in PubMed or other databases, to further document the arguments in the scientific literature. The two research questions for this review were specifically for our research area, i.e., the fields of oncology and radiological biology. However, the majority of arguments obtained are general in nature and can thus be applied to other fields, such as in chemotherapy, microbiology, infectiology, etc. (86-88). This review thus not only presents arguments about the use of animals for oncology and radiological biology, but clarifies pertinent arguments for and against the use of animals for medical experiments in general.

## CONCLUSION

This critical review highlighted six arguments for and eleven arguments against the use of animal experimentation in medicla research, using the method proposed by McCullough, Coverdale and Chervenak (30,31). The arguments for animal testing are based on the similarity between humans and animals, on the good that animal testing can do, on the moral difference between animals and humans, on tradition as well as scientific relevance, on economic contribution and on prudence for animal welfare. Most of the argument against animal experiments are a direct response to the arguments for animal testing. In addition to these, the arguments put forward are based on the impediment of progress through the use of animals, on the harm done to humans, on transferability, on the limits of the scientific community and on the protection of democracy. The arguments against animal testing are, in our view, more convincing not only from an ethical point of view, but also and above all from a scientific point of view. For that reason, we recommend the use and acceptability of non-animal, human-relevant methods to improve data generation pertinent to human health. On the basis of this critical review, we argue that research not only in oncology and radiobiology but in medicine in general should comply with the 3Rs principles. To achieve this, healthcare sectors must undertake a paradigm shift in the education future researchers and clinicians, so that the use of animal-free alternatives becomes the most important R to strive towards. Furthermore, greater education and training is needed on the relevance of the 3Rs principles for members of funding agencies and elected government representatives, so that they base their decisions on a well informed and rational understanding of the issues raised by the use of animal experimentation when the use of alternatives is feasible. More than 60 years after the publication of the 3Rs principles, it is time that we finally focus on human relevance (89) and move beyond the tradition that drives animal model selection in research (90). The conservative culture that dominates medical research harms not only animals, but also humans, by delaying scientific discoveries that are relevant and appropriate to humans.

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