

No clear trends in expatriation of non-human primate research from Switzerland between 2004 and 2017

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Keine klaren Trends bei der Abwanderung der Primatenforschung aus der Schweiz zwischen 2004 und 2017

Tierversuche werden weltweit häufig in der wissenschaftlichen Forschung eingesetzt. Weltweit anerkannte Standards der ethischen Grundlagen oder anerkannte Tierversuch Praktiken fehlen. Zwischen den Ländern bestehen große Unterschiede. Ein kürzlich veröffentlichter Bericht vermutet, dass einige Forscher, insbesondere aus Ländern mit strengeren Tierversuchsvorschriften, die experimentelle Forschung in Länder mit weniger strengen Vorschriften verlagern könnten. Mittels einem systematischen Literaturreview wurden wissenschaftliche Publikationen untersucht, die auf Tierversuchen mit Primaten und von Arbeitsgruppen mit Sitz in der Schweiz basierten. Es wurde die P3 Datenbank «Projects People Publications» vom Schweizerischen Nationalfonds (SNF) verwendet, um SNF finanzierte Forschungsprojekte mit Primaten von Schweizer Forschungsgruppen zu identifizieren. Das Web of Science wurde mit dieser Namensliste gemeinsam mit Begriffen aus der Primatenforschung durchsucht. Publikationen ohne Autor einer Schweizer Institution, Freilandstudien oder retrospektive Studien an verstorbenen Primaten und nicht-originale Forschungsarbeiten wurden ausgeschlossen. Für jede Veröffentlichung haben wir den Versuchsort, die Finanzierungsquelle, Tieranzahl, Art und Tierversuchsbewilligung erfasst. Wir übernahmen 120 Veröffentlichungen mit mehr als 2,429 Tieren in den Review. *Macaca mulatta* und *Macaca fascicularis* waren die häufigsten Arten. Ein zunehmender Trend der Verlegung von Primatenversuchen ausserhalb der Schweiz konnten wir nicht bestätigen. Im Laufe der Studienzeit wurde die Angaben zur Tierversuchsbewilligung konsistenter aufgeführt. Diese Ergebnisse sollten mit Vorsicht interpretiert werden, da der vorliegende Review nur Studien umfasste, die: 1) veröffentlicht und 2) im Web of Science veröffentlicht wurden. Folglich wurden Studien mit unbedeutenden Ergebnissen oder von geringer Qualität möglicherweise ausgeschlossen, weil diese Studien selten veröffentlicht oder oft in Zeitschri-

Abstract

Animal experimentation is commonly practiced in scientific research worldwide. However, there are no globally accepted standards for regulating the ethical boundaries and accepted practices for animal experimentation. Large differences exist between countries. A report suggested that some researchers, especially from countries with more stringent animal experimentation regulations, may be relocating experimental research to countries with less stringent regulations. We followed a systematic literature review approach to identify publications and determine whether there is an increasing trend in expatriation of non-human primate experimentation by researchers based in Switzerland. We used the Projects People Publications database, which contains projects funded by the Swiss National Science Foundation, to identify researchers conducting experiments using non-human primates. This list of names, together with terms referring to non-human primates were used to search the Web of Science. Publications without an author affiliated to a Swiss institution, no living or only with free non-human primates, and non-original research were excluded. For each publication, we recorded the place of experimentation, funding source, number of animals, species and the statement of ethical approval. We retained 120 publications, involving more than 2,429 non-human primates. *Macaca mulatta* and *Macaca fascicularis* were the most common species. We could not confirm an increasing trend in expatriation of non-human primate experimentation outside of Switzerland. Over time, publications appeared to report the ethical approval number more consistently. These results should be interpreted with caution because the sample included only studies that were: 1) published and 2) reported in the Web of Science. Consequently, studies with insignificant results may have been excluded because these studies are rarely published, and studies of poor quality may have been excluded because they are often published in lower quality journals, not indexed by the Web of Science.

Key words: Animal experimentation, expatriation, non-human primates, Switzerland, trend

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ten von geringerer Qualität ausserhalb des Web of Science veröffentlicht werden.

Schlüsselwörter: Tierversuche, Verlegung, Primaten, Schweiz, Trend

Introduction

Animal experimentation is a well-established method that is used worldwide in many areas of biomedical research. Ethical issues around animal experimentation have generated intense debate in the scientific community and society, as scientific knowledge and changing societal norms have influenced the perception of animal experimentation. While during the 20th century there was a sharp increase in the number of animals used in scientific research, there was also an increased recognition of animals as sentient beings and a continued debate on the moral implications of animal experimentation.^{4,12} This led to the development of laboratory animal science, the recognition of the importance of animal welfare, the development of the Three Rs Principles (Reduce, Refine, Replace)⁴⁴ and to a progressive demand for more transparency, stricter regulations or bans on certain types of experiments.^{13,21,22,28} More recently, several journals adopted frameworks for better reporting of animal experiments, such as the «Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) Guidelines»,^{19,32} or the «Planning Research and Experimental Procedures on Animals: Recommendations for Excellence (PREPARE)».^{30,38} Platforms for the preregistration of animal experiments such as «Preclinicaltrials.eu»²⁹ have been established and statements, such as the «Basel Declaration», were endorsed by researchers.²⁶

Animal experimentation is still commonly seen as an essential element in some research fields, however there is debate about continuing to use this kind of experimentation in the future.^{23,26} Attitudes towards animal experimentation vary greatly between countries, social groups and in respect to the concerned animal species and characteristics of research.^{9,13,31} In many European and North American countries, some species of non-human primates are of special concern, especially when it comes to more invasive experiments.^{14,46}

There are no worldwide animal welfare standards, regulations or laws for the justification, conduct, limitation and reporting of animal experiments. Significant variation exists between countries.⁴³ Some countries have well defined and enforced laws and regulations. In others, legislation does not exist, does not cover all species used in experiments within the country, or there may be no enforcement capacity.^{16,48} Official

reporting of animal experiments also varies between countries. It ranges from no reporting of any information about animal experimentation conducted within the country to some countries that publish detailed statistics about the number of animals used.⁴¹ In countries with robust legislation, stringent animal welfare standards and strong public concerns about animal experiments, the relocation of animal experiments and researchers outside the country has become a topic of concern.^{7,16,19}

Over the years there has been a trend of increasing numbers of international collaborations between scientists from different countries.²⁴ At least in some of these collaborations, not all experiments are funded by the same agency and they may be implemented in different countries. Collaborations are generally positive and may lead to better harmonization of standards and regulations between countries.⁴⁵ But, it is important to recognize that this does not always happen and in some cases animal experiments are relocated to avoid regulations or prohibitions, something that can be referred to as «ethics dumping», a practice which naturally worries funding agencies and the general public.^{7,36}

The present study was conducted in Switzerland, where the animal welfare legislation relies on the recognition of the dignity of animals – including those enrolled in laboratory experiments – and requires a careful weighing of interests.⁴² Animal experiments can only take place if no alternative method is available, after carefully weighing of the harms and benefits and if the husbandry meets the minimal requirements for the concerned species, based on current knowledge about its biology and behavior.^{35,36} In Switzerland, the number and species of animals used for experimentation, the purpose of animal experiments and the degree of severity of animal experiments are reported and publicly communicated annually by the Federal Food Safety and Veterinary Office (FSVO).⁵ Legal disputes around experiments with non-human primates have occurred and certain licenses to perform these experiments were revoked by local courts or the Federal Supreme court.³⁹ Along with regulations, public and political pressure against animal experimentation may lead some researchers in Switzerland to shift their non-human primate experiments to other countries with more permissive regulations.^{1,8,39} The purpose of our study was to deter-

mine whether non-human primate experimental research by researchers based in Switzerland has been shifted out of the country. We used a systematic literature review approach to identify publications reporting non-human primate experimental research by researchers based in Switzerland and assessed whether there were trends in: 1) location of experimentation, 2) ethical standards reported in these publications and 3) the number of non-human primates used in experiments.

Materials and Methods

Researcher Selection

To identify researchers based in Switzerland engaged in animal experimentation, we used the Projects People Publications (P3) database of the Swiss National Science Foundation (SNSF).⁴⁰ It contained 2487 grants funded by the SNSF for the years between 2001 and 2016. None of the projects using non-human primates had a starting date before 2004.

Literature Search

We followed a systematic literature review approach to identify publications using the Web of Science (WoS) database⁴⁷ on the 7th of March 2018, with the «Advanced Search» function and two search queries performed sequentially. The first query consisted of the project applicants' names that were extracted from the P3 database, in the field tag «AU» (author) combined with the Boolean term «OR». In the second query, the field tag «TS» (topic) included the following species names: «ape\$ OR baboon\$ OR bonobo\$ OR Callithrix jacchus OR chimpanzee\$ OR gorilla\$ OR guenon\$ OR Hominidae OR Macaca fascicularis OR macaque\$ OR Maccaca mulatta OR marmoset\$ OR monkey\$ OR orangutan\$ OR Pan\$ OR Papio\$ OR Pongo\$ OR primate\$ OR Rhesus macaque\$ OR tamarin\$ OR vervet\$ monkey\$ OR vervet\$ OR Cercopithecus OR Callimico goeldii OR Simia diana». The two queries were then combined, using the Boolean term «AND», under the «Combine sets» option. The search was restricted to publications in English, classified as «Articles», within the «Time-span» from 2004 to 2017.

The search in the WoS identified 574 publications. One duplicate was removed. Publications then were examined by the first author and excluded for the following reasons: 1) none of the authors was affiliated to a Swiss institution and the publication did not report funding from an institution based in Switzerland ($n=138$); 2) publications were classified as literature reviews ($n=21$); 3) no living non-human primates were used ($n=137$); 4) all the animals involved were wild and in natural reserves or natural habitat ($n=140$); and 5) publications were multiple reports from the same experiment ($n=17$).

Publications were classified as multiple reports from the same experiment if the same animal(s) and experimental protocol(s) were identified in different publications. When this was the case, the report with the earliest date of publication was selected for the study and all others excluded. After exclusion 120 publications remained (Figure 1).

Data extraction

From each selected publication, we extracted information about the place of experimentation, number and species of animals used, ethical standards reported and funding organization(s). In most publications this information was extracted from the Material and Methods, Notes or Acknowledgement sections. In some cases, it was extracted from other sections or the supplementary materials. Each publication was then classified according to the place of experimentation, the ethical standards reported and the degree of severity (zero or greater).

The place of experimentation was classified into four categories: 1) «Switzerland», if the publication reported experiments conducted or approved only in Switzerland; 2) «Switzerland and Outside», if the publication reported experiments conducted or approved in both Switzerland and another country or countries; 3) «Outside», if the publication reported experiments conducted or approved exclusively outside of Switzerland; 4) «No statement», if there was no information reported about the place of experimentation or approval. In publications where the

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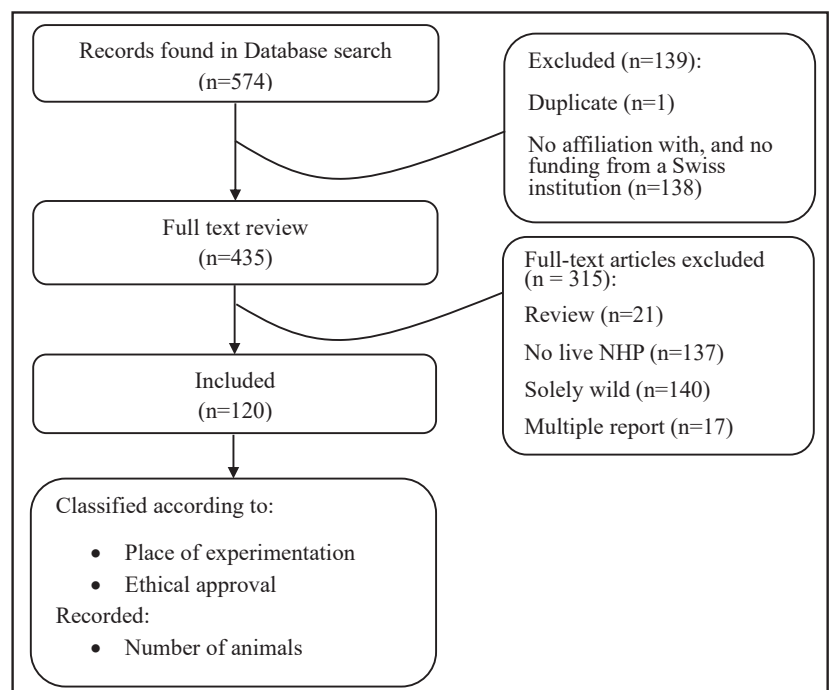


Figure 1: Flow chart of the process followed during the literature search for data extraction.

Table 1: Mann-Kendall Trend test for percentage of articles from each place of experimentation published between 2004 and 2017. Reported are the tau and p values.

| Place of experimentation | Mann-Kendall Trend test tau values (τ) | p |
|--------------------------|---|-------|
| Switzerland | 0,134 | 0,545 |
| Switzerland and Outside | 0,418 | 0,054 |
| Outside | 0,034 | 0,912 |
| No statement | -0,625 | 0,003 |

Table 2: Mann-Kendall Trend test for the percentage of animals in each place of experimentation between 2004 and 2017. Reported are the tau and the p values.

| Place of experimentation | Mann-Kendall Trend test tau values (τ) | p |
|--------------------------|---|-------|
| Switzerland | -0,165 | 0,443 |
| Switzerland and Outside | 0,408 | 0,056 |
| Outside | -0,243 | 0,250 |
| No statement | -0,512 | 0,015 |

Table 3: Mann-Kendall Trend test for the percentage of publications with degree of severity above 0, in different places of experimentation between 2004 and 2017. Reported are the tau and the p values.

| Degree of severity | Place of experimentation | Mann-Kendall Trend test tau values (τ) | p |
|--------------------|--------------------------|---|-------|
| 0 | Switzerland | -0,023 | 0,956 |
| Above 0 | Switzerland | 0,057 | 0,875 |
| 0 | Switzerland and Outside | 0,542 | 0,013 |
| Above 0 | Switzerland and Outside | 0,200 | 0,807 |
| 0 | Outside | 0,115 | 0,636 |
| Above 0 | Outside | 0,232 | 0,333 |
| 0 | No statement | - | - |
| Above 0 | No statement | -0,377 | 0,179 |

Table 4: Tau and p-values from the Mann-Kendall Trend Test for the percentage of manuscripts published between 2004 and 2017, for each category of ethical standards reported and for the total reporting approval (sum of «Approval Number» and «Approval») and total not reporting approval (sum of «Guidelines followed» and «No statement»). Reported are the tau and the p values.

| Ethical standards reported | Mann-Kendall Trend test tau values (τ) | p |
|------------------------------|---|-------|
| Approval Number | 0,451 | 0,037 |
| Approval | -0,326 | 0,123 |
| Guidelines followed | -0,155 | 0,497 |
| No statement | -0,314 | 0,170 |
| Total reporting approval | 0,284 | 0,184 |
| Total not reporting approval | -0,284 | 0,184 |

places of experimentation and approval were different, the place of experimentation was the one considered.

The ethical standards reported were classified in four categories: 1) «Approval Number» if the ethical approval

number was reported; 2) «Approval» if the article reported having received approval for the experiment, but an approval number was not reported; 3) «Guidelines Followed» if no approval was reported, but the authors reported having followed guidelines; 4) «No statement» if no statement about approval or guidelines followed was reported. In case two different ethical standards' categories were reported, the publication was classified based on the category with the lowest level of ethical approval, using the following ranking: highest level – reporting of the approval number >> reporting that the experiment was approved >> reporting solely having followed guidelines >> no statement. Publications were also divided in two groups – reporting approval and not reporting approval. The first included all publications classified as «Approval Number» and «Approval» and the second those classified as «Guidelines followed» and «No statement».

Each article was then classified as degree of severity zero or greater, based on the definitions for experimental degree of severity provided by the FSVO.¹¹ We classified all experiments in manuscripts reporting multiple experiments and chose the highest classification of degree of severity.

Finally, we classified publications into 3 funding categories: 1) publications reporting funding received from Swiss institutions, if all or part of the funding came from at least one Swiss Institution; 2) publications reporting funding exclusively received from non-Swiss institutions; 3) publications not reporting any information about funding sources.

Analysis

Data compilation was done using Microsoft Excel.²⁷ Data management, bar charts and analysis were performed using the statistical software R V.3.5.2.³⁴ The non-parametric Mann-Kendall Trend test, performed with the R package «Trend»,³³ was used to assess the existence of monotonic trends in the total number of articles and animals and, to consider fluctuations of publications between different years, in the annual percentages of articles classified in the different categories over the years of publication. The threshold of statistical significance was set at 0.05. Time trend lines (loess smoothing) were plotted for each category analyzed.

Results

Number of publications, animals and species used

There were 120 publications with more than 2429 non-human primates, for the years between 2004 and

2017, included in the study. From these, 623 animals were from zoos. The number of animals reported in each study varied from 1 to 309. There was a statistically significant increasing trend in the number of articles published between 2004 and 2017 ($\tau=0,484$ $p=0,0249$), accompanied by a significantly increasing trend in the number of animals reported in these studies ($\tau=0,685$, $p<0,001$) (Figure 2 and Figure 3). Two publications, both from 2006, did not report the number of animals used, but all publications reported the species. The year with the highest number of animals was 2014. This was due to a large study including 309 animals (50,0% of the total recorded in that year) with a degree of severity zero. Rhesus monkeys (*Macaca mulatta*) and crab-eating macaques (*Macaca fascicularis*) were the most commonly used species, one or both being present in 71 (59,2%) publications. Twenty-seven (22,5%) publications involved more than one species. Other species included: Barbary macaque (*Macaca sylvanus*), black-headed spider monkey (*Ateles fusciceps*), black lemur (*Eulemur macaco*), brown capuchin (*Sapajus apella*), bonobos (*Pan paniscus*), Bornean Orangutan (*Pongo pygmaeus*), chimpanzee (*Pan troglodytes*), common marmoset (*Callithrix jacchus*), common squirrel monkey (*Saimiri sciureus*), coppery titi (*Plecturocebus cupreus*), cotton-top tamarin (*Saguinus oedipus*), crowned lemur (*Eulemur coronatus*), Diana monkey (*Cercopithecus diana*), eastern lesser bamboo lemur (*Hapalemur griseus*), emperor tamarin (*Saguinus imperator*), gelada (*Theropithecus gelada*), Geoffroy's spider monkey (*Ateles geoffroyi*), golden lion tamarin (*Leontopithecus rosalia*), golden-headed lion tamarin (*Leontopithecus chrysomelas*), Gracile capuchin (*Cebus apella*), Goeldi's monkey (*Callicebus goeldii*), green monkey (*Chlorocebus sabaensis*), Hamlyn's monkey (*Cercopithecus hamlyni*), Japanese macaque (*Macaca fuscata*), L'Hoest's monkey (*Cercopithecus lhoesti*), lion tamarin (*Leontopithecus chrysomelas*), mandrill (*Mandrillus sphinx*), mantled guereza (*Colobus guereza*), pileated gibbon (*Hylobates pileatus*), pied tamarin (*Saguinus bicolor*), red ruffed lemur (*Varecia rubra*), ring-tailed lemur (*Lemur catta*), ruffed lemur (*Varecia variegata*), siamang (*Symphalangus syndactylus*), sooty mangabey (*Cercocebus atys*), southern pig-tailed macaque (*Macaca nemestrina*), Sumatran Orangutan (*Pongo abelii*), Tonkean macaque (*Macaca tonkeana*), tufted capuchin (*Sapajus apella*), Verreaux's sifaka (*Propithecus verreauxi*), western gorilla (*Gorilla gorilla*), white-faced saki (*Pithecia pithecia*), white-headed marmoset (*Callithrix geoffroyi*) and white-lipped tamarin (*Saguinus labiatus*).

Places of experimentation

Forty-three (35,8%) publications, involving 622 (25,6%) non-human primates were classified as «Switzerland» (Figure 4). Nineteen (15,8%) publications, involving 952 (39,2%) animals, were classified as «Switzerland and Outside» (Figure 5). Thirty-eight (31,7%) publications, involving 768 (31,6%) animals, were classified as «Out-

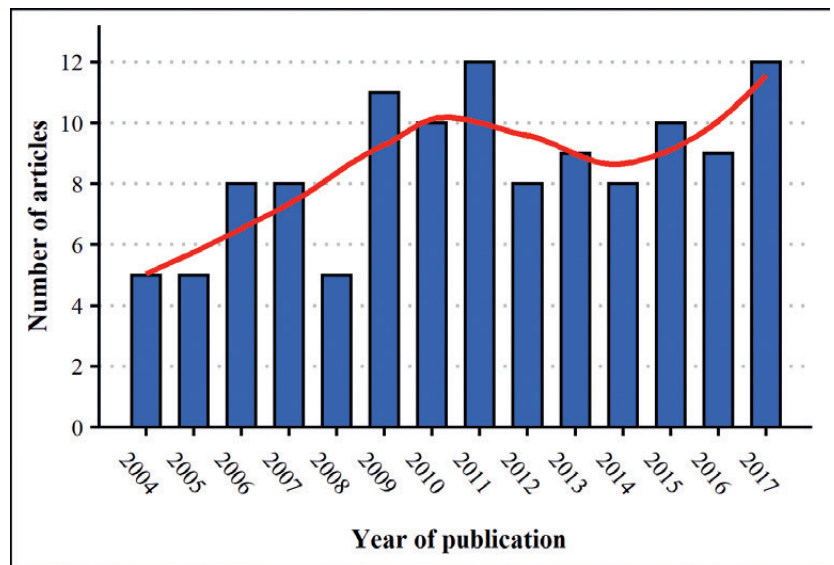


Figure 2: Bar chart with the number of articles included in the study by year of publication between 2004 and 2017. A loess smoothed trend line is shown in red.

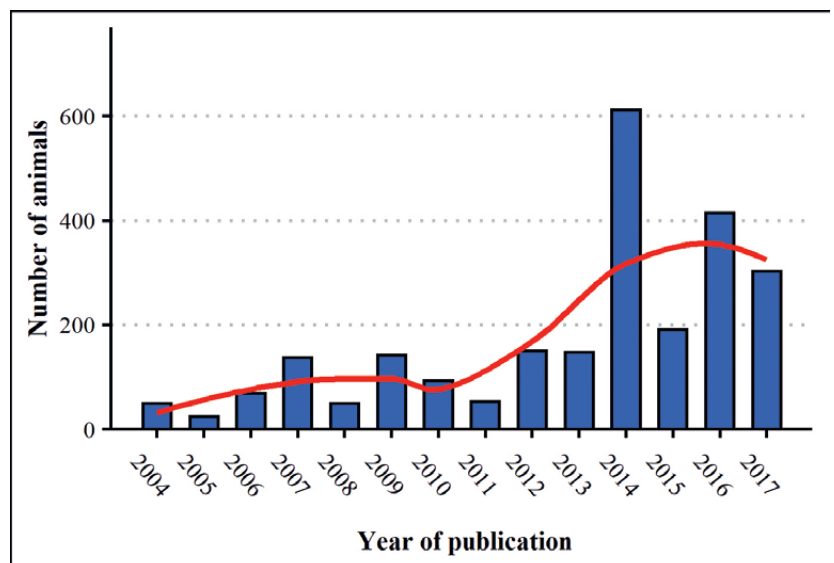


Figure 3: Bar chart with the total number of animals used by researchers per year of publication between 2004 and 2017. A loess smoothed trend line is shown in red.

side of Switzerland» (Figure 6). Twenty (16,7%) publications, involving 87 (3,6%) animals, were classified as «No statement» (Figure 7). From the 19 publications classified «Switzerland and Outside», 10 (52,6%) involved animals from zoos.

For place of experimentation, the only statistically significant trend found was a decrease in the percentage of publications classified as «No statement» ($\tau=-0,625$, $p=0,003$) (Figure 6 and Table 1).

The publications classified as «Outside» and «Switzerland and Outside» included experiments performed in

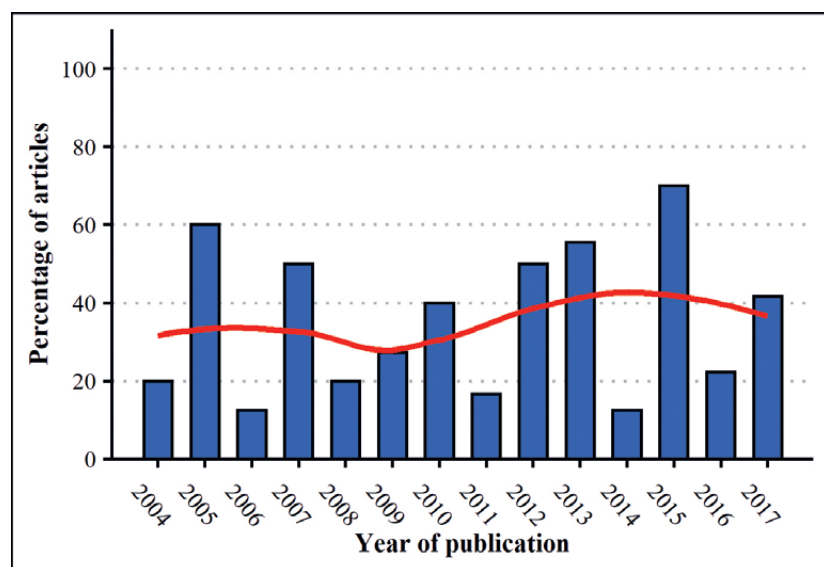


Figure 4: Bar chart of the percentage of manuscripts published between 2004 and 2017 classified as «Switzerland» regarding the place of experimentation. A loess smoothed trend line is shown in red.

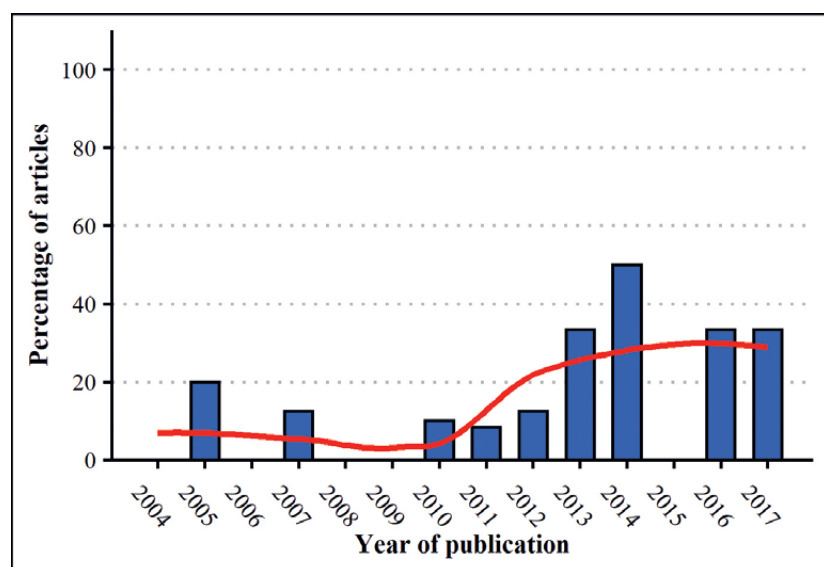


Figure 5: Bar chart of the percentage of manuscripts published between 2004 and 2017 classified as «Switzerland and Outside» regarding the place of experimentation. A loess smoothed trend line is shown in red.

18 different countries. Six in Austria, three in Belgium, three in China, one in Czech Republic, one in Denmark, five in France, 13 in Germany, one in Israel, five in Italy, one in Mexico, five on the Netherlands, four in Saint Kitts, two in Spain, one in Sweden, six in the United Kingdom and 22 in the United States of America. Nineteen (15,8%) publications reported experiments done in more than one country.

Consistently, for the percentage of animals used in each category of place of experimentation, the only statistically significant trend was a decrease in the percentage

of animals from publications classified as «No statement» ($\tau = -0,512$, $p = 0,015$) (Table 2).

Degree of severity

Forty-three (35,8%) publications, involving 1735 (71,4%) non-human primates were classified as degree of severity zero and 77 (64,2%) publications, involving 694 (28,6%) animals were classified as degree of severity greater than zero. Among studies with degree of severity zero, 20 (46,5%) were classified as «Switzerland», 12 (27,9%) as «Switzerland and Outside», 10 (23,3%) as «Outside of Switzerland» and one (2,3%) as «No statement», regarding the place of experimentation. Among the studies with degree of severity greater than zero, 23 (30%) were classified as «Switzerland», seven (9,1%) as «Switzerland and Outside», 28 (36,4%) as «Outside of Switzerland» and 19 (24,7%) as «No statement», regarding the place of experimentation. The only statistically significant trend was an increase in the percentage of publications classified as «Switzerland and Outside» with a degree of severity zero ($\tau = 0,542$, $p = 0,013$) (Table 3).

Ethical standards reported

Twenty-six (21,7%) publications, involving 737 (30,3%) non-human primates, reported an ethical approval number. Sixty-nine (57,5%) publications, involving 1339 (55,1%) animals, reported having been approved but did not provide a number. Eighteen (15%) publications, involving 194 (8,0%) animals, reported following guidelines. Seven (5,8%) publications, involving 159 (6,5%) animals, reported no statement about approval. One publication reported conducting an experiment in a country other than the country where approval was issued.

The only statistically significant trend found was an increase in the percentage of publications reporting an ethical approval number ($\tau = 0,451$, $p = 0,037$) (Figure 8). When the percentage of publications was divided in two groups – the total reporting approval («Approval Number» and «Approval») and total not reporting approval («Guidelines followed» and «No statement») – no statistically significant trend was found (Table 4).

Sources of Funding

Eighty-six publications (71,7%) reported having been totally or partly funded by institutions based in Switzerland. From these, 79 (65,8%) stated funding from the SNSF. Twenty-eight publications (23,3%) reported funding only from institutions based in other countries. Six publications (5,0%) did not report any funding institutions.

Discussion

We found no evidence to support the hypothesis that researchers based in Switzerland have increased the

amount of research conducted in other countries during the study period. When analyzing separately experiments with degree of severity zero and above zero, we found no evidence for significant trends, with exception of a rising trend in the publications with degree of severity zero classified as «Switzerland and Outside» ($\tau=0,542, p=0,013$). We also found an increasing trend in the reporting of details relating to the ethical approval and the location of experimentation or approval. Over the study period there was an overall increase in the number of manuscripts published. The temporal trend in the number of animals used followed similar patterns, with an overall increase in the number of animals. We consider these findings to be important for Swiss society and funding agencies, such as the SNSF.

We identified some experiments conducted abroad. This is not unusual, as it has also been reported in other countries^{8,15} and it is not surprising in Switzerland, where international scientific collaborations are considered strategic and promoted by the Federal Council of Switzerland. Various funding agencies, including the SNSF, offer grants aimed at establishing international collaborations or for international scientific stays. Experiments conducted outside of Switzerland, or both in Switzerland and other countries, may, at least in part, be a result of these international collaborations. We observed publications with multiple authors based in different countries and funded by different organizations. However, these data were not systematically recorded. The contribution of each author was seldom reported, making it impossible to determine the role played in the study. It is noteworthy that based on the criterion «Protecting animals used in scientific research», within the indicator of «Presence of animal welfare legislation» of the Animal Protection Index, Austria, Denmark, France, Netherlands and Sweden have similar scores to Switzerland. Consequently, shifting experiments to these countries most likely would not be a result of regulatory constraints.

Overall, ninety-five (79,2%) publications reported receiving ethical approval for all the experimental protocols, which is equal to the proportion reported by Yoon *et al.*⁵⁰ We observed an increasing trend in the reporting of specific ethical approval, which may indicate better reporting transparency. Among the 26 publications reporting this number, 23 (88,5%) were published after 2012. Eighteen (90%) of the 20 publications classified as having «No statement» for the place of experimentation were published before 2012. These findings may reflect an increasing endorsement of the ARRIVE Guidelines. Since their publication in 2010, the ARRIVE guidelines emphasize the need for reporting information on ethical approval of animal experiments.¹⁹ However, some authors pointed out that following the ARRIVE guidelines is still far from universal.^{3,18}

Within our sample, two (1,7%) publications, from 2006, did not report the number of animals used in the study. In contrast, Carlsson *et al.* reported in 2004 that 63% did not report the number of animals in the study⁶ and Kilkenny *et al.* reported in 2009 that all publications reported the number of non-human primates used.²⁰ The discrepancy among these findings may be due to differences in study designs. The first included studies using «some type of primate biological material», while the second included only experiments with live primates. Our study included studies with live primates or where primates were euthanised for the study. Our fin-

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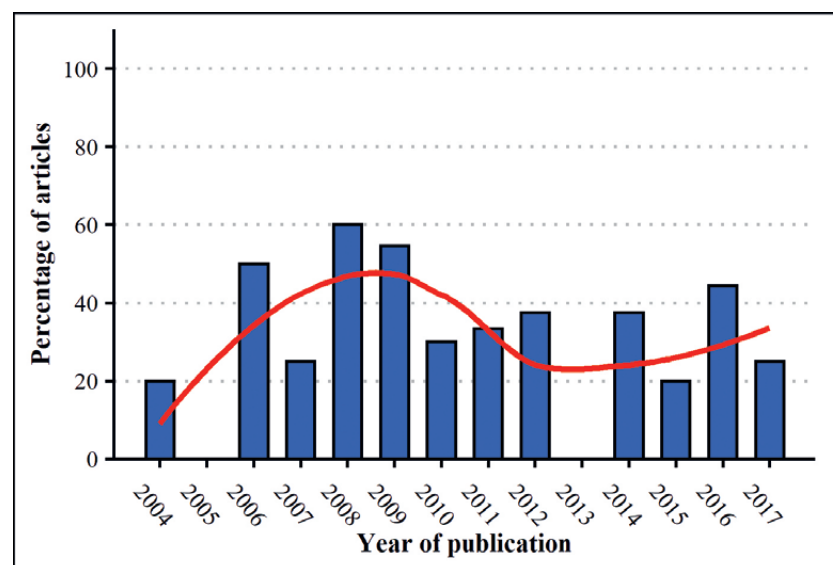


Figure 6: Bar chart of the percentage of manuscripts published between 2004 and 2017 classified as «Outside of Switzerland» regarding the place of experimentation. A loess smoothed trend line is shown in red.

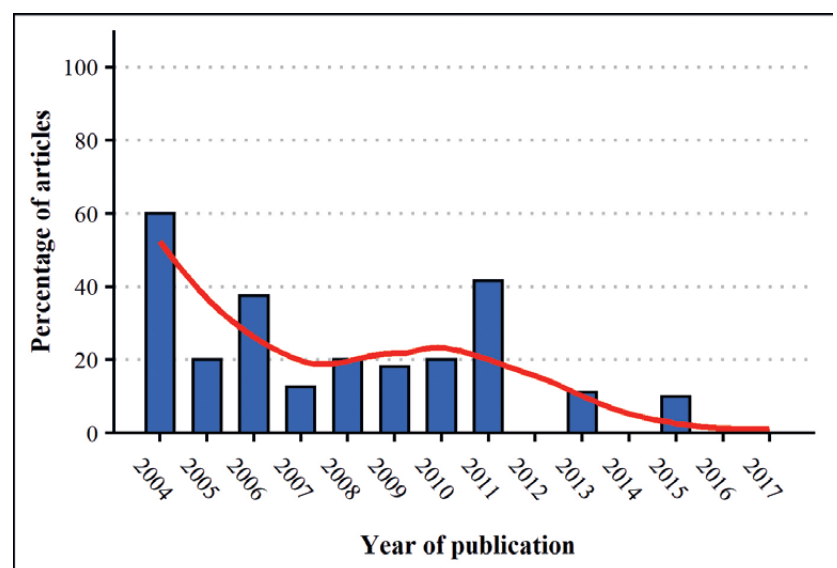


Figure 7: Bar chart of the percentage of manuscripts published between 2004 and 2017 classified as «No statement» regarding the place of experimentation. A loess smoothed trend line is shown in red.

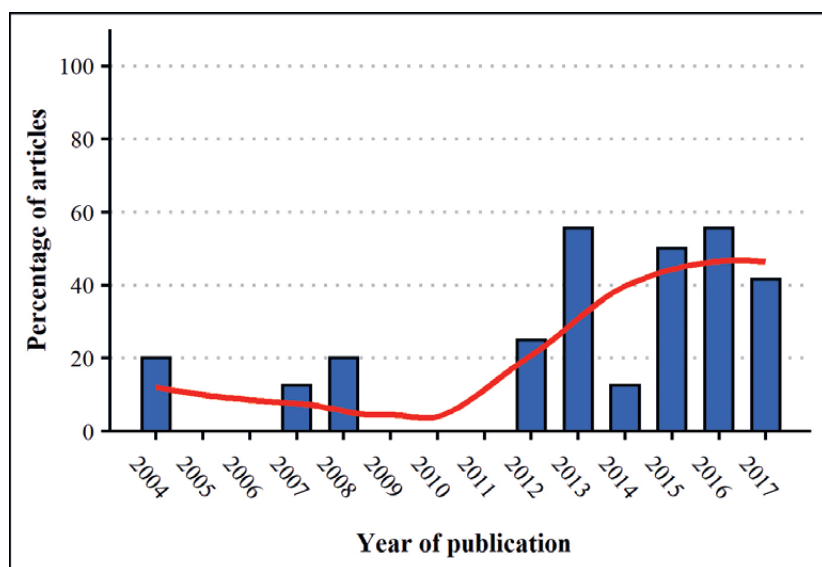


Figure 8: Bar chart of the percentage of manuscripts published between 2004 and 2017 reporting the approval number. A loess smoothed trend line is shown in red.

ding that *Macaca mullata* and *Macaca fascicularis* were the most common species involved in experiments is in agreement with the findings from other studies focused on non-human primate experimental research conducted in Canada, the USA and Sweden.^{6,15,23}

In nine (7,5%) of the publications in our study, authors reported double affiliation, one being a Swiss institution and the other being an institution outside of Switzerland. These publications did not report receiving funding from a Swiss funding agency. The experimental location in five of these publications was reported to be outside of Switzerland and the other four had no information about the location. It could be that these authors were in transit from an institution outside of Switzerland to a Swiss institution, or vice versa, or had a permanent double affiliation.

The present study has limitations and should thus be interpreted with caution. It is possible that, by relying uniquely on SNSF P3 database to identify researchers working with non-human primates in Switzerland, we introduced some bias towards basic academic research. Even if for this branch of science the SNSF is an important public funding agency,⁴⁹ it is not the only one and it is possible that some researchers have never been funded by SNSF for experiments with non-human primates, especially if they work in corporate research and development. Furthermore, for the approval of funding, the SNSF requires the experiments to be performed in places with similar animal welfare conditions to those of Switzerland. This requirement makes it more difficult for researchers to shift experiments to places with lower standards and less regulations. Relying exclusively on a

single database (WoS) may have resulted in not identifying some studies published in non-listed journals. In addition, relying uniquely on published experiments may have introduced further bias, as it has been suggested that negative or non-significant results are less likely to be published.^{10,25,37} This is of concern, as poorly planned studies without ethical approval may not be published, or may be published in poorly cited journals not included in the WoS. Finally, the time lag between the actual experiment and the publication of the results may have resulted in some of the experiments conducted during the investigated interval not being included.

In several studies it was not easy to find information on the place of experimentation or role played by each researcher. This influenced our classification of publications. In studies where place of experimentation was not reported, we used the country of ethical approval as place of experimentation, if stated. One article reported the country of experimentation at a different location than the country where the approval was issued. It was not possible to identify the reasons why some researchers applied for ethical approval in one country and conducted their research in another. However, we feel that it would be important for researchers to be transparent about this and report their reasons. Journal editors and reviewers could play a role by requesting this information from authors. This also emphasizes the importance of complete and transparent reporting of ethical statements, including the place where experiments are performed and roles and contributions of each author.

It was our opinion that experiments with degree of severity greater than zero may be more likely to be expatriated. For this reason we tested the publications classified as degree of severity zero and greater than zero separately, per place of experimentation, for the presence of a trend. The reason behind an increasing trend for the percentage of articles classified as «Switzerland and Outside» and degree of severity zero could be, at least in part, studies with zoo animals. More than half (52%) of these publications involved animals from zoos, so these studies were expected to be mainly observational and therefore, to have a low degree of severity. This would be in accordance with a report of the increase in studies with zoo animals, namely primates, over the previous years.¹⁷ The lack of other trends could also be due, at least in part, to the small sample size, as there were only a few articles with degree of severity greater than zero per place of experimentation each year, along 14 years.

Unfortunately, it is difficult to have an accurate picture on the real complete trend, due to reasons presented above. The numbers reported by the FSVO show a significant decrease in the number of primates used in experiments in Switzerland with a degree of severity one

to three, for the years between 2004 and 2017, but no statistically significant trend in the number of animals involved in experiments with a degree of severity zero.⁵ In our study we recorded the total number of animals per year of publication. However, our results cannot be compared with FSVO reported numbers, as in our study there were several publications classified as «Switzerland and Outside» or «No statement» and two of the articles did not report the number of animals involved. In the future, other approaches could consider monitoring these trends and trying to understand what the main reasons behind the decrease were. Changes in legislation and court rulings may have had an important influence on the trends. But we believe that the ultimate cause – abandoning certain animal experiments, expatriation of experiments or shifting to another country – cannot be fully confirmed using uniquely the quantitative approach we employed.

Good animal welfare standards, strict regulations and transparency are important, not just from a scientific perspective, but also from a moral and a social perspective. Monitoring changes in animal experimentation helps assuring researchers, funding bodies, legislators and the general public that regulations are respected and effective and can prompt debates about procedures and legislation. Non-human primates represent just a small

proportion of the total number of animals used for experimentation.⁶ It would be interesting to verify our findings with a more comprehensive systematic literature review of further repositories and grey literature to determine whether the same trends apply to other animal species. It is also important to understand the role and motivations of researchers who are based in Switzerland, but conduct their research outside the country.

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The authors declare that they have no competing interests.

Author contributions statement

SR, JB and FMS conceived and designed the study; SR and FMS acquired and collected the data; SR, JB and FMS analysed and interpreted the data; FM wrote the first draft; all authors revised and approved the final version.

No clear trends in expatriation of non-human primate research from Switzerland between 2004 and 2017

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Aucune tendance claire à l'expatriation de Suisse de la recherche sur les primates non humains entre 2004 et 2017

L'expérimentation animale est couramment pratiquée dans la recherche scientifique dans le monde entier. Cependant, il n'existe pas de normes mondialement acceptées pour réglementer les limites éthiques et les pratiques acceptées pour cette expérimentation. De grandes différences existent entre les pays. Un rapport récent a suggéré que certains chercheurs, en particulier provenant de pays où la réglementation sur l'expérimentation animale est restrictive, pourraient délocaliser la recherche expérimentale vers des pays où les réglementations sont moins strictes. Nous avons suivi une approche de revue systématique de la littérature pour identifier les publications et déterminer s'il y a une tendance croissante à l'expatriation des expérimentations sur les primates non humains par des chercheurs basés en Suisse. Nous avons utilisé la base de données Projects People Publications, qui contient des projets financés par le Fonds national suisse de la recherche scientifique pour identifier des chercheurs conduisant des expériences sur des primates non humains. Cette liste de noms, ainsi que les termes faisant référence à des primates non hu-

Nessuna chiara tendenza nell'espatrio della ricerca sui primati non umani dalla Svizzera tra il 2004 e il 2017

La sperimentazione animale è comunemente praticata nella ricerca scientifica in tutto il mondo. Tuttavia, non esistono standard accettati a livello internazionale per regolamentare i limiti etici e le pratiche accettate per la sperimentazione animale. Esistono grandi differenze tra i differenti Paesi. Un recente rapporto ha suggerito che alcuni ricercatori, in particolare provenienti da Paesi con normative più severe sulla sperimentazione animale, potrebbero trasferire la ricerca sperimentale in Paesi con normative meno severe. Per questo studio abbiamo seguito un approccio di revisione sistematica della letteratura per identificare le pubblicazioni e determinare se vi è una tendenza crescente nell'espatrio della sperimentazione di primati non umani da parte dei ricercatori in Svizzera. Abbiamo utilizzato la banca dati Projects People Publications, che contiene progetti finanziati dal Fondo nazionale svizzero per la scienza, al fine di identificare i ricercatori che conducono esperimenti utilizzando primati non umani. Questo elenco di nomi, insieme ai termini che si riferiscono a primati non umani, è stato utilizzato per effettuare ricerche nel Web of Science. Sono state escluse le pubblicazioni senza auto-

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mains ont été utilisés pour effectuer des recherches sur le Web of Science. Les publications sans auteur affilié à une institution suisse, non vivant ou consacrées uniquement à des primates non humains libres ainsi que les travaux de recherche non originaux ont été exclus. Pour chaque publication, nous avons enregistré le lieu d'expérimentation, la source de financement, le nombre d'animaux, les espèces et la déclaration d'approbation éthique. Nous avons retenu 120 publications, impliquant plus de 2,429 animaux. *Macaca mulatta* et *Macaca fascicularis* étaient les espèces les plus communes. Nous n'avons pas pu confirmer une tendance à la hausse de l'expatriation en dehors de la Suisse des expérimentations sur des primates non humains. Au fil du temps, les publications semblent déclarer le numéro d'approbation éthique de manière plus cohérente. Ces résultats doivent être interprétés avec prudence car l'échantillon ne comprenait que des études 1) publiées et 2) rapportées dans le Web de la science. Par conséquent, les études avec des résultats non significatifs peuvent avoir été exclues car ces études sont rarement publiées et les études de mauvaise qualité peuvent avoir été exclues car elles sont souvent publiées dans des revues de moindre qualité, non indexées par le Web of Science.

Mots clés: Expérimentation animale, expatriation, primates non humains, Suisse, tendance

re affiliato a un'istituzione svizzera, senza primati non umani deceduti o liberi, e ricerche non originali. Per ogni pubblicazione, abbiamo registrato il luogo della sperimentazione, la fonte di finanziamento, il numero di animali, la specie e la dichiarazione di approvazione etica. Abbiamo preso in considerazione 120 pubblicazioni che coinvolgono più di 2,429 animali. *Macaca mulatta* e *Macaca fascicularis* erano le specie più comuni. Non abbiamo potuto confermare una tendenza in aumento nell'espatrio della sperimentazione sui primati non umani al di fuori della Svizzera. Nel corso del tempo, le pubblicazioni sembravano riportare il numero di approvazione etica in modo più coerente. Questi risultati devono essere interpretati con cautela perché il campione includeva solo studi che erano: 1) pubblicati e 2) riportati nel Web of Science. Di conseguenza, gli studi con risultati insignificanti potrebbero essere stati esclusi perché questi studi sono pubblicati raramente, gli studi di scarsa qualità potrebbero essere stati esclusi perché sono spesso pubblicati su riviste di qualità inferiore e non indicizzate dal Web of Science.

Parole chiave: sperimentazione animale, espatrio, primati non umani, Svizzera, tendenza

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