DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

July 12, 2023

Re: Animal Welfare Assurance
A3304-01 [OLAW Case 4B]

Dana L. Director, Ph.D.
Vice President of Research Administration
and Senior Staff Officer
Oregon Health and Science University
3181 SW Sam Jackson Park Rd. - MC: L335
Portland, OR 97239

Dear Dr. Director,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your June 28, 2023 letter in response to allegations of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Oregon Health & Science University (OHSU) and the affiliated Oregon National Primate Research Center (ONPRC). These allegations were received from Physicians Committee for Responsible Medicine. The allegations did not describe specific incidents of noncompliance at the university nor at ONPRC. This office has requested a description of your institution's processes or procedures for performing a search for alternatives to live vertebrates and a description of the processes or procedures utilized by the IACUC to ensure research involving live vertebrates is not duplicative.

Per your letter, it is understood justification for the use of live animals includes the following processes:

- Pre-proposal review of requests for animal allocation by the Animal Utilization Committee (AUC) of the ONPRC.
- Proposal review by a panel of national scientific experts.
- A search and review of current literature and potential alternatives by the investigator during IACUC animal use protocol preparation.
- Oversight by the IACUC in review of justification for the use of live animals.

It is stated that during monthly meetings, the AUC reviews research proposals and determines if allocation of nonhuman primates is consistent with the 7th edition of the *National Primate Research Center Guidelines*. Regarding proposals that do not undergo a formal external peer reviewed process, these proposals must be reviewed by the Research Advisory Committee (RAC). It is also stated that only when a proposal is approved by the AUC and the RAC (when required), then an investigator may submit a proposal to fund work conducted at the ONPRC. Investigators that receive permissions from the ONPRC AUC and RAC to pursue funding and secure an award, must also justify the use of live animals to the IACUC.

The IACUC is composed of members from various backgrounds, including veterinarians, a behaviorist, a librarian, and biosafety officer. It is stated all members of the committee appreciate the scarcity of animal resources and the ethical responsibility to conduct live animal experimentation only when alternative methods are not suitable. Investigators must conduct a literature search for alternatives using a minimum

of two scientific databases. Also, searches must cover a minimum of 3 years but frequently include the past 10 years, per the letter. It is understood the librarian serving on the IACUC can assist investigators in the conduct of an appropriate literature search.

Investigators must justify the use of live animals when alternatives are not available by answering a series of questions. Investigators must explain the benefits to society and the advancement of scientific knowledge and explain how estimated animal numbers were determined. It is stated statistical analyses, data from previous experimental results, or references to published research are required as well. Investigators must address the 3R's and attest their due diligence in assuring the work is not duplicative or they must justify why it is necessary to validate results of previously performed experiments.

Thank you for the detailed responses to OLAW's concerns. Based on its assessment of this explanation, OLAW understands that the Oregon Health & Science University and ONPRC have appropriate processes and procedures in place to perform a search for alternatives to live vertebrates and ensure research involving live vertebrates is not duplicative. We find no cause for further action by this Office.

Sincerely,

Jacquelyn T. Tubbs -S

Digitally signed by Jacquelyn T. Tubbs -S
Date: 2023.07.12 09:27:39 -04'00'

Jacquelyn Tubbs, DVM, DACLAM
Senior Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact
Aaron Rhyner, DVM, Acting Director of Animal Welfare Operations

A3304-4B

OHSU

OHSU Research & Innovation

(b) (6)

Dana Director, PhD
Vice President of Research Administration & Senior Staff Officer

director@ohsu.edu
www.ohsu.edu/research

Mail code: L335
3181 S.W. Sam Jackson Park Rd.
Portland, OR 97239-3098

June 28, 2023

Jacquelyn T. Tubbs, DVM, DACLAM
Senior Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817

RE: Case A3304-4B

Dear Dr. Tubbs,

Thank you for this opportunity to explain how the Oregon Health & Sciences University (OHSU) and the Oregon National Primate Research Center (ONPRC) ensure that both the research involving live vertebrate animals is not duplicative, and that live animal models are only used when non-animal models would be inadequate to answer the scientific hypotheses of the research. While some demographic studies in humans may provide anecdotal data, live animals are required as models in tightly controlled experiments to answer hypothesis-driven research that cannot be conducted with human subjects or non-animal models. We welcome this opportunity to describe how our institution complies with the PHS Policy through rigorous review and oversight of live animal experimentation by our Institutional Animal Care and Use Committee (IACUC).

Justification for the use of live animals involves a series of critical reviews; these reviews start with a pre-proposal review of requests for animal allocation by the Animal Utilization Committee (AUC) of the ONPRC, are then followed by proposal review by a panel of national scientific experts, then require a search and review of current literature and potential alternatives by the investigator during IACUC animal use protocol preparation, and conclude with thorough oversight by the IACUC in review of justification for the use of live animals. The IACUC's review includes, but is not limited to, assessment of the minimal number of live animals needed to answer critical questions, as well as evaluation of procedural advancements to reduce the use of live animals, refine procedures to minimize pain and distress, and replace live animal models with alternatives.

Rigorous review begins early in the planning process for all studies that propose the use of nonhuman primates. ONPRC's AUC is charged with allocation of scarce animal

resources to only the most promising and impactful scientific inquiries. The AUC is composed of ONPRC Division Chiefs who are leading experts in their fields of scientific inquiry, Directors of NHP Resource Programs, the Attending Veterinarian, the ONPRC Center Director and Associate Directors, and additional subject matter experts as requested. The AUC meets monthly to rigorously review research proposals and determine if allocation of nonhuman primates is consistent with the 7th edition of the *NPRC (National Primate Research Center) Guidelines.* If a proposal will not be reviewed through a formal external peer review process as required for all NIH and government funded research, the proposal must be reviewed by the Research Advisory Committee (RAC). The RAC discusses submissions quarterly, or more frequently as needed, and is chaired by the Associate Director of Research with representatives from each scientific Division at ONPRC as well as a scientist from OHSU's Marquam Hill and Waterfront Campuses. Only when approved by the AUC, and the RAC when required, may an investigator submit a proposal to fund work conducted at the ONPRC.

The IACUC recognizes the external review process for funding and considers it part of the review for scientific merit and for avoiding duplicity of research. Specifically, external subject matter experts serving on Scientific Review Panels for the funding agencies assess proposals for the most appropriate models to answer the scientific questions. Highly competitive proposals are ranked for their potential to advance knowledge and only studies with the highest scientific merit are successfully awarded funds.

Once the investigator has attained permissions from the ONPRC AUC and RAC to pursue funding and an award has been secured, the investigator must justify the use of live animals to the IACUC. The ONPRC IACUC comprises 14 voting members representing five scientific divisions of the ONPRC. In addition to the members from the five divisions, there are two members from the OHSU Research Integrity Office, two veterinarians, a behaviorist, a biosafety officer, a librarian, and two non-scientific members, one who is not affiliated with the institution in any way other than as a member of the IACUC. Ten alternate members serve on the IACUC, routinely attend meetings, contribute to protocol reviews, and join in the discussions but do not vote. The members bring a wide variety of perspectives to the review process and actively engage in deliberation. IACUC meetings occur monthly for a three-hour period with all initial studies using non-human primates discussed during full committee review. The committee reaches a decision to approve, require additional changes to gain approval, or withhold approval on proposed activities. Discussions continue until decisions are reached, typically unanimously.

All members of the IACUC have appreciation for the scarcity of animal resources and the ethical responsibility to conduct live animal experimentation only when alternative methods are not adequate. The investigator is required to conduct a literature search for alternatives using at least two scientific databases. Investigators are provided a hyperlink in the protocol form to the Animal Welfare Information Center (AWIC) as a resource in best practices for conducting a search for alternatives. The searches must cover at least three years but typically include the past 10 years. Keywords used in the search strategy must be listed and the results of the search must be described in the electronic protocol form presented to the IACUC. The librarian serving on the IACUC can assist investigators in conducting appropriate literature searches.

The investigator must also address a series of questions describing the overall objectives of the project, justifying the use of live animals only when alternatives are not available, explaining the benefits to society and the advancement of scientific knowledge, and explaining how estimated animal numbers were determined. Statistical analyses, data from previous experimental results, or references to published research are required to justify the number of animals requested.

In addition, the investigator must justify the use of live animals by thoroughly answering the following three questions to address the 3 Rs;

- "Provide the scientifically justified rationale for using animals as opposed to tissue culture, micro-physiological systems, clinical human studies, instructional media aids, or other alternative methods;"
- "Explain how experimental procedures and/or changes to the animal(s) experimental environment have been refined or enhanced to minimize pain or distress;"
- "Explain how the experimental paradigm has been developed to assure that the minimum number of animals will be used to obtain scientifically valid results and to maximize the information obtained from a given number of animals (without increasing pain or distress);"

Finally, the investigator, who is the subject matter expert, must attest their due diligence in assuring the work is not duplicative or they must justify why it is necessary to validate results of previously conducted experiments.

As requested and avoiding conflict of interest, we reviewed the allegations of inadequate oversight, improper searches for alternatives, and duplication of prior research according to the IACUC's *Policy for Review and Reporting of Animal Welfare*

Concerns and found the charges to be unsubstantiated. The IACUC considers their role in animal research oversight to be of the utmost importance and takes this responsibility seriously. The members of the committee, the investigators, and the veterinarians and husbandry personnel who care for the animals are committed to providing the highest quality of welfare for the animals. The work conducted with the precious non-human primates at the ONPRC is rigorously reviewed with respect for the animals, the ethical allocation of scarce animal resources, and commitment to research to improve the lives of both humans and animals.

Sincerely.

(b) (6)

Dana Director, Ph.D.
Vice President for Research Administration & Senior Staff Officer
Institutional Official

A3304-4B

McCoy, Devora (NIH/OD) [E]

From: McCoy, Devora (NIH/OD) [E]
Sent: Wednesday, June 28, 2023 3:59 PM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: response to case A3304-4b

Good afternoon (b) (6)

Thank you for this additional information for case A3304-4B and we will send an official response soon.

Best,
Devora

Devora McCoy, BS, MBA (pronunciation)
Program Analyst
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Phone: 301-435-2390
Email: devora.mccoy@nih.gov

From: (b) (6)
Sent: Wednesday, June 28, 2023 3:36 PM
To: McCoy, Devora (NIH/OD) [E] <devora.mccoy@nih.gov>
Cc: Dana Director <director@ohsu.edu>; (b) (6)
Subject: [EXTERNAL] response to case A3304-4b

Dear Dr. Tubbs,
Please find attached a response to allegations from PCRM regarding Oregon Health & Science University, case A3304-4B. Please do not hesitate to contact me if I can provide further information.

Respectfully,

(b) (6)

A3304-46

PhysiciansCommittee
for Responsible Medicine

5100 Wisconsin Ave. NW, Suite 400 | Washington, DC 20016 | Tel: 202-686-2210 | Fax: 202-686-2216 | PhysiciansCommittee.org

May 2, 2023

Robert Gibbens, DVM
Director, Animal Welfare Operations
USDA/APHIS/Animal Care
2150 Centre Ave.
Building B, Mailstop 3W11
Fort Collins, CO 80526-8117

Patricia A. Brown, V.M.D., M.S.
Director, Office of Laboratory Animal Welfare
National Institutes of Health
RKL 1, Suite 360, MSC 7982
6705 Rockledge Dr.
Bethesda, MD 20892-7982

Submitted by email (brownp@od.nih.gov; robert.m.gibbens@aphis.usda.gov)

Re: Use of Animals for Human Dietary Research at Oregon National Primate Research Center

Dear Dr. Gibbens and Dr. Brown:

The Physicians Committee for Responsible Medicine requests that the United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) and the National Institutes of Health's (NIH) Office of Laboratory Animal Welfare (OLAW) investigate the Oregon National Primate Research Center's repeated use and killing of numerous non-human primates to study maternal and child health outcomes that could have been studied using humans and human-relevant approaches.

The Oregon National Primate Research Center cannot justify its use of animals to study a common human diet that could be easily and ethically studied in consenting human volunteers. These uses of animals run afoul of the Animal Welfare Act's mandate that experiments be "designed to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research." Human nutrition research using non-human primates is a step backward in terms of scientific relevance. The use of animals here demonstrates both a lack of scientific merit and research misconduct under the Animal Welfare Act.

The Physicians Committee believes that inadequate oversight by Oregon National Primate Research Center's Institutional Animal Care and Use Committee (IACUC) and by extension Oregon Health & Science University, is responsible for the improper approval and ongoing use of live animals for human health research.

Use of Animals to Study Human Health and Behavior is not "Scientifically Valuable Research"

Section 2143 of the Animal Welfare Act and C.F.R. Title 9, Section 2.31(e) of the Animal Welfare Act's

implementing regulations state that a proposal to conduct an activity involving animals must describe "procedures designed to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research."

Using non-human primates to understand developmental and reproductive effects of human nutrition is not a scientifically valuable line of research. The factors in the studies described below have been or can readily be studied in humans. The Oregon National Primate Research Center's animal use here is convoluted and at odds with the current standards of practice in human behavioral and nutritional research in the United States. As detailed below, dietary interventions are frequently studied by collecting data from humans via clinical trials, observational studies, and surveys.

Study 1

In a 2022 publication titled "Maternal Western-style Diet Reduces Social Engagement and Increases Idiosyncratic Behavior in Japanese Macaque Offspring" by Mitchell et al., researchers at the Oregon National Primate Research Center used macaques to examine the relationship between maternal consumption of "Western-style" diet and offspring social behavior. [1]

Researchers fed captive adult female and male Japanese macaques either a control diet or a diet with a macronutrient composition that models the "Western-style" diet for at least one year prior to pregnancy. One hundred and sixty-four adult females bred with adult males and the Novel Peer Introduction behavioral assessment was administered to 39 infants at 6.6 months of age to quantify time spent engaging in social interactions. Researchers employed path models to associate maternal diet and third trimester factors (maternal metabolic and inflammatory alterations) to offspring social behaviors. Adiposity, intravenous glucose tolerance testing, cytokine panel, and blood were collected while pregnant primates were sedated during their third trimester.

The authors admit that an association between maternal body mass index and risk of childhood neurodevelopmental disorders has already been established in humans but that "a limited number of preclinical studies have examined associations between maternal "Western-Style Diet exposure and offspring social behavior."

The authors further conclude that "these results provide evidence that maternal consumption of Western-style diet during gestation may be linked to an increased risk of neurodevelopmental disorders and provides targets for prevention and intervention efforts." As discussed below, there is substantial clinical evidence showing that human maternal diet is associated with altered social behavior in offspring rendering animal experiments, sometimes euphemistically referred to as "pre-clinical" studies) unnecessary.

Numerous peer-reviewed studies demonstrate the equivalence or superiority of human-biology-based models to examine the relationship between maternal consumption of "Western-style" diet and offspring behavior. For example:

- A longitudinal study selected 1,580 mother-child pairs to examine the relationship between maternal dietary patterns and offspring cognition.[2]

- Researchers assessed maternal diet during pregnancy, performed cognitive and behavioral assessments on children at three time points (infancy, early childhood, and mid-childhood), and completed a validated 23-item questionnaire from parents and teachers designed to assess social, emotional, and behavioral functioning.

- A study of 7,814 mother-offspring pairs found that an unhealthy diet during pregnancy was associated with higher levels of child emotional-behavioral dysregulation.[3]

- A data analysis from 23,020 mothers during pregnancy and their children at 1.5, 3, and 5 years of age found that higher consumption of unhealthy foods prenatally predicted externalizing problems among children independent of childhood diet or other confounding variables.[4]

- An evaluation of 4,094 mother-child pairs found that maternal pre-pregnancy obesity is associated with increased offspring peer relationship problems and a 30-70% higher likelihood of offspring behavioral problems by.[5]

- A longitudinal study recruited 4,165 women to participate in the Generation R Study that followed children from fetal life into childhood, investigating maternal inflammation and autistic traits (e.g., communication and social behavior deficits) at 6 years old.[6]

- A prospective cohort study within an overarching study investigating brain development and outcomes in preterm infants from 2007 to 2010 assessed 62 obese and non-obese mothers and preterm infants to investigate the association between obesity and infant neurodevelopment.[7] Infants had an MRI at the age they would have been born had they not been premature and returned for developmental testing at 2 years old. The authors found that maternal obesity was associated with a positive screen for autism and lower language scores.

Study 2

The NIH grants (MH107508 and MH117177) that funded Study 1 also funded "Maternal Diet and Obesity Shape Offspring Central and Peripheral Inflammatory Outcomes in Juvenile Non-Human Primates" by Dunn and researchers (2022), which examined how maternal "Western-style" diet affected neurological inflammation in offspring.[8] Researchers fed captive adult female and male Japanese macaques either a control diet or a diet with a macronutrient composition that models the "Western-style" diet for at least one year prior to pregnancy. Experimenters used infant primates from Study 1. The infants stayed with their mothers and were weaned at around 8 months of age, after which experimenters fed the infants either a control diet or a "Western-style" diet. At around 13 months, corresponding to 3-4 years old in humans, 24 infant primates were killed so that their brains could be collected, and brain tissue analyzed for inflammation. The state and welfare of the mothers were not reported. The authors concluded that maternal diet and fat content may predict offspring's brain and inflammation levels, and that the mother's fat content levels predicts peripheral inflammation in infants.

Inflammatory markers can easily be measured in humans from simple blood testing and correlations with diet can be established. Doing so in humans allows for research that is free of the confounders inherent in experiments on nonhuman species.

Other studies demonstrate the availability of human-biology-based models to examine the

relationship between maternal consumption of "Western-style" diet and offspring inflammatory outcomes. For example:

- A study measured 25 inflammatory proteins indicative of peripheral and central inflammatory responses in three separate blood samples (day 1, day 7, and day 14) from 939 infants born to obese and non-obese women.[9] Their findings suggest that a mother's pre-pregnancy overweight appears to contribute to a prolonged inflammatory state in certain preterm infants.

Study 3

In "Individual and Combined Effects of 5-Year Exposure to Hyperandrogenemia and Western-style Diet on Metabolism and Reproduction in Female Rhesus Macaques," Bishop et al. (2021) used at least 35 female rhesus macaques aged about 2 and a half years old to model the impact of long-term exposure to "Western-style" diet in women with polycystic ovary syndrome (PCOS) in the post-partum period. Researchers placed them in four groups: group one received cholesterol implants and control diet; group two received testosterone implants and control diet; group three received cholesterol implants and a "Western-style" diet; and group four received testosterone implants and a "Western-style" diet.[10] Cholesterol served as a vehicle control. Testosterone implants were used in an attempt to approximate the elevated hormone levels that occur in many women with PCOS. The study duration was five years. In year four, female macaques bred and had their fetuses killed and removed by Caesarean section in their third trimester. Due to the experimental conditions, some of the macaques were not able to carry their pregnancies until the third trimester. The trial continued for another year and "animals were bled daily for 30 days at 5 years." Researchers concluded that "Western-style" diet exposure altered ovarian cycles and increased body weight and body fat.

Because PCOS is a common condition in humans, it has been extensively studied. To the extent further research is needed regarding diet and PCOS, it can and should be done ethically in humans so as to avoid the confounders caused by the use of a nonhuman species, and artificial model of PCOS, and artificial diets.

Other studies demonstrate the equivalence or superiority of human-biology-based models to examine consumption of "Western-style" diet by women with PCOS. For example:

- A study evaluated the effect of lactation on insulin resistance, glucose and insulin metabolism, sex hormone-binding globulin (protein), and insulin-like growth factor binding protein-1 concentrations in women who are fully breast-feeding with and without PCOS during the postpartum period and after weaning.[11] Twelve lactating PCOS women and six non-PCOS lactating women of similar age and BMI were selected, and measurements were collected. The authors found that in women with PCOS insulin resistance is not modified during lactation and that lactation has a transitory beneficial effect on insulin levels and biological markers of insulin resistance.

- A study of lifestyle interventions for patients with systematically investigated long-term changes in PCOS symptoms throughout pregnancy and postpartum.[12] The study

systematically investigated 64 women using structured interviews about lifestyle changes over 10 years, created a detailed hormone profile of these women and carried out vaginal ultrasound to calculate ovarian scores. The study found that pregnancy and parenthood may have an impact on long-term course of PCOS; women with children reported shorter cycles and had lower testosterone levels compared to women without children.

Study 4

"Maternal Western Diet Exposure Increases Periportal Fibrosis Beginning in Utero in Nonhuman Primate Offspring," by Nash et al. (2021), researchers examined maternal obesity and the mechanisms of nonalcoholic fatty liver disease in offspring. Researchers used more than 100 adult female Japanese macaques who were made obese through eating a "Western-style" diet over the course of two to nine years before becoming pregnant and throughout pregnancy.[13] At advanced stages of their pregnancy, the mother's fetuses were surgically removed and killed so their livers could be excised. Other female macaques in the study endured at least one additional pregnancy. In these cases, some of the fetuses were killed immediately following surgery, but experimenters killed others a year later so their livers could be taken and analyzed. The state and welfare of the mothers were not reported. The authors concluded that modifying diet in women prone to obesity or weight gain could prevent or delay the onset of pediatric nonalcoholic fatty liver disease (NAFLD), and that altering the mother's diet or supplementing her diet with resveratrol reduced markers of fibrosis, oxidative stress, and fetal hypoxemia.

Dietary behavior and hepatic health can readily be assessed in humans. Simple blood tests measure a variety of endpoints regarding the health of the liver. Noninvasive scans and ultrasound play adjunctive roles.

Other studies demonstrate the equivalence or superiority of human-biology-based models to examine the mechanisms of nonalcoholic fatty liver disease. For example:

- A longitudinal study examined the influence of infant nutrition and maternal obesity on the risk of non-alcoholic fatty liver disease (NAFLD) in 1,170 adolescents and performed a non-invasive ultrasound to evaluate the effects on the participant's livers.[14] The authors found that maternal pre-pregnancy obesity is associated with NAFLD in adolescent offspring and that breastfeeding initiated at birth and continued for 6 months or longer before starting infant formula milk reduces the odds of NAFLD in adolescence. These measures, along with a normal body mass index in mothers before pregnancy, reduces the risk of NAFLD.

Study 5

"The Combined Impact of Testosterone and Western-Style Diet on Endometriosis Severity and Progression in Rhesus Macaques," Bishop et al. examined how PCOS and an obesogenic diet impact the progression of endometriosis. The experimenters fed 39 female macaques either a standard diet for macaques or a "Western-style" diet for seven years.[15] Experimenters gave female macaques either testosterone to approximate the hyperandrogenemia characteristic of PCOS in women or cholesterol as a control. All macaques underwent laparoscopic procedures that collected adipose

tissue and liver biopsies and single and multiple ovarian follicles, and uterine biopsies. They had at least one C-section in their third trimester of pregnancy. All macaques had at least one surgical procedure involving the reproductive tract before diagnosis. All females were killed at the end of the study. The authors concluded that metabolic disturbances are associated with exposure to androgens in the presence of a "Western-style" diet and are correlated with onset of cystic endometriosis in rhesus macaques. The authors stated that endometriosis observed in women with PCOS may be related to alterations in metabolic status, and not androgen exposure alone.

This is a highly artificial study, since it does not study PCOS directly, but rather an attempt to simulate it in monkeys. As in the previous studies, dietary behavior and the relevant physiological endpoints can readily be studied in humans.

Other studies demonstrate the availability of human-based methods for studying the impact of diet on the female reproductive tract. For example:

- A study examined how four different diet plans affected ovarian morphology in 111 women with PCOS. Ultrasound, blood samples, and dietary screening were employed. The authors found that certain diets improved the appearance of the ovaries, reduce insulin resistance, dysglycemia, hyperandrogenism, and obesity, and caused satiety and weight loss in women.[16]

- Twenty-six women diagnosed with a) female infertility for various reasons, including polycystic ovary syndrome and endometriosis, and b) body mass index considered overweight or obese, were included in a randomized block-design controlled trial where they were either placed in a low glycemic index group or a control group.[17] The objective of the study was to determine the relationship between diet and pregnancy rate in overweight and obese infertile women undergoing the process of *in vitro* fertilization. The authors found that a hypocaloric low glycemic index diet promoted a decrease in body mass index, percentage of body fat and the hormone leptin concentrations, which further improved oocyte development and pregnancy rate.

- A pilot feasibility study recruited 8 women with PCOS to determine whether a low glycemic index diet would reduce risk factors for endometrial cancer in high-risk women compared with conventional hypocaloric diet.[18] Clinical assessments, blood tests, pelvic ultrasound scans, and endometrial biopsies were employed.

1. Oregon National Primate Research Center's Justification of Animal Use is Insufficient Because Alternatives Exist

Section 2143 of the Animal Welfare Act and C.F.R. Title 9, Section 2.31(d)(1)(i, ii) of the Animal Welfare Act's implementing regulations require that the principal investigators consider alternatives to procedures that may cause more than momentary or slight pain or distress to any animal used for research or educational purposes.

The PIs did not meet this requirement because there is no rationale for animal use given the abundance of clinical research examining these interventions. As demonstrated in the previous

section, a proper alternatives search would have revealed nonanimal methods for these experiments and numerous peer-reviewed literature demonstrating the equivalence or superiority of human-biology-based models compared to animal use.

3. The Use of Animals for Human Health and Behavioral Research is "Duplicative" and Not "Unavoidable"

The Animal Welfare Act requires that activities involving animals be designed to "assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research." 9 C.F.R. § 2.31(e)(4). Further, the investigator must assure that "the activities do not unnecessarily duplicate previous experiments." C.F.R. § 2.31(d)(iii).

The Principal Investigators did not meet these requirements because numerous clinical trials have already studied and reported the effects of these interventions (maternal "Western-style" diet, social behavior, reproductive health) on many endpoints in humans. Such use of live animals is duplicative and avoidable.

4. Oregon National Primate Research Center's IACUC Is Failing to Properly Oversee Animal Use

Section 2143 of the Animal Welfare Act and Title 9, Section 2.31(d)(1)(i, ii) of the Animal Welfare Act's implementing regulations require that the IACUC enforce the requirements described in items 1 through 3 above and thereby determine that the proposed activities are in accordance with the Animal Welfare Act and C.F.R Title 9, Section 2.31(d).

The Oregon National Primate Research Center's IACUC did not meet these requirements because the animal use protocol was approved despite the shortcomings described above.

5. PHS Policy and the *Guide*

Finally, the issues described above violate the PHS Policy and the *Guide for the Care and Use of Laboratory Animals* (the *Guide*). OLAW must evaluate allegations of noncompliance with the PHS Policy "and, as necessary, restrict or withdraw approval of [Animal Welfare] Assurances."

The PHS Policy's Principle II of the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training emphasizes that "procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society." Principle III provides that "the animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered."

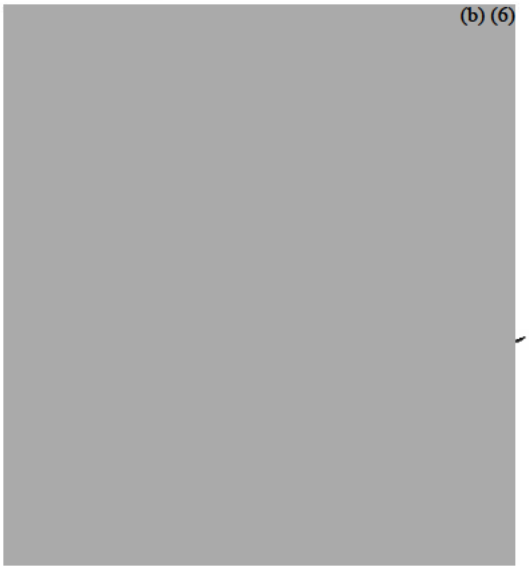
The *Guide* states that the "use of laboratory animals for biomedical research, testing and education is guided by the principles of the Three Rs" and explicitly endorses "consideration of alternatives…to reduce or replace the use of animals" and "use of appropriate species."

As detailed above, non-human primates were not an appropriate species here as the subjects of inquiry have been extensively and safely studied in humans.

Accordingly, the Physicians Committee requests that APHIS and OLAW investigate this matter and order corrective action and appropriate penalties.

Thank you for your attention.

Sincerely,



References

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DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

May 16, 2023

Re: Animal Welfare Assurance
A3304-01 [OLAW Case 4B]

Dana L. Director, Ph.D.
Vice President of Research Administration
and Senior Staff Officer
Oregon Health and Science University
3181 SW Sam Jackson Park Rd. - MC: L335
Portland, OR 97239

Dear Dr. Director,

The Office of Laboratory Animal Welfare (OLAW) has received from Physicians Committee for Responsible Medicine allegations of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Oregon Health & Science University (OHSU) and the affiliated Oregon National Primate Research Center (ONPRC).

The allegations do not include specific incidents of noncompliance at the university or ONPRC. The organization describes the use of nonhuman primates as a model to study maternal and child health nutrition outcomes at the ONPRC. It is stated that inadequate oversight by the IACUC has resulted in improper approval and ongoing use of live animals for human nutrition research. It is also stated that a proper search for alternative to animals would have revealed experimental methods that do not utilize animal models and included peer-reviewed articles demonstrating the equivalence/superior models based on human biology.

As authorized under section V. A. 4. of the PHS Policy, and as referenced in your Animal Welfare Assurance for Humane Care and Use of Laboratory Animals, OLAW is requesting that your institution provide an explanation regarding these concerns. Please describe your institution's processes/procedures for performing a search for alternatives e.g., computational, invertebrate, in vitro, etc. to live vertebrates as models for research. Please describe processes/procedures utilized by the IACUC to ensure research involving live vertebrates is not duplicative.

Please instruct the IACUC, avoiding any conflict of interest, to investigate these allegations and if substantiated but not previously reported to OLAW, please state why not. Please also provide further information regarding the incident(s) and all corrective/preventive actions. If PHS/NSF-funded, please report the applicable grant/contract number.

We appreciate your cooperation and ask that you please provide the requested information **by June 30, 2023**. Please contact me if I can be of assistance at jacquelyn.tubbs@nih.gov.

Sincerely,

Jacquelyn T. Tubbs -S

Digitally signed by Jacquelyn T. Tubbs -S
Date: 2023.05.16 15:24:21 -04'00'

Jacquelyn Tubbs, DVM, DACLAM
Senior Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact

A3304-4B

McCoy, Devora (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Thursday, May 4, 2023 8:53 PM
To: McCoy, Devora (NIH/OD) [E]
Cc: Tubbs, Jai (NIH/OD) [E]
Subject: FW: [EXTERNAL] Use of Animals for Human Dietary Research at Oregon National Primate Research Center

Follow Up Flag: Follow up
Flag Status: Completed

Hello Devora,

Please use this email to open a case for the ONPRC (under A3304). Please assign it to Dr. Tubbs. Thank you.

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov>
Sent: Tuesday, May 2, 2023 3:59 PM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Subject: FW: [EXTERNAL] Use of Animals for Human Dietary Research at Oregon National Primate Research Center

Dear Brent,

Please review this additional information from Physicians Committee for Responsible Medicine.

Sincerely,

Pat

Patricia Brown, VMD, MS, DACLAM (she/her)
Director, Office of Laboratory Animal Welfare,
Office of Extramural Research, Office of the Director, NIH
301-451-4209, brownp@mail.nih.gov

From: [redacted] (b) (6)
Sent: Tuesday, May 2, 2023 2:50 PM
To: robert.m.gibbens@aphis.usda.gov; Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov>
Cc: Adrian.Lindsey@usda.gov; agsec@usda.gov
Subject: [EXTERNAL] Use of Animals for Human Dietary Research at Oregon National Primate Research Center

Robert Gibbens, DVM
Director, Animal Welfare Operations
USDA/APHIS/Animal Care

2150 Centre Ave.
Building B, Mailstop 3W11
Fort Collins, CO 80526-8117
robert.m.gibbens@aphis.usda.gov

Patricia A. Brown, V.M.D., M.S.
Director, Office of Laboratory Animal Welfare
National Institutes of Health
RKL 1, Suite 360, MSC 7982
6705 Rockledge Dr.
Bethesda, MD 20892-7982
brownp@od.nih.gov

Re: Use of Animals for Human Dietary Research at Oregon National Primate Research Center

Dear Dr. Gibbens and Dr. Brown:

The Physicians Committee for Responsible Medicine, a national nonprofit with more than 17,000 doctor members, filed a complaint with the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) and the Office of Laboratory Animal Welfare (OLAW) at the National Institutes of Health today, May 2, 2023, about five research studies at the Oregon National Primate Research Center that the group says violated the Animal Welfare Act.

The Primate Research Center, part of Oregon Health & Science University (OHSU), has repeatedly used and killed hundreds of nonhuman primates, including infants, along with hundreds of nonhuman primate fetuses, to study maternal and child health nutrition outcomes that could have been studied ethically and effectively in humans.

The federal law governing animals used in research says discomfort and pain to animals should be limited to that which is unavoidable for the conduct of scientifically valuable research. These nutrition studies retreat from the species of interest (humans), the Physicians Committee's complaint says, to examine nonhuman primates—a step backward in terms of scientific relevance that demonstrates both a lack of scientific merit and research misconduct under the Animal Welfare Act.

The Oregon National Primate Research Center's cruel and inhumane practice of confining, breeding, and killing hundreds of monkeys, including infants and fetuses, to study the developmental and reproductive effects of human nutrition violates the Animal Welfare Act since pain, discomfort, and death of the animals is avoidable. Because the research objectives have been or can readily be studied in humans, such use of live animals is duplicative and needless.

A proper search for alternatives to animal experimentation, as required by the Animal Welfare Act, would have revealed experimental methods that do not use animals and numerous peer-reviewed articles demonstrating the equivalence or superiority of models based on human biology.

At federally funded research institutions, any use of live animals for research, testing, or training must be approved by the Institutional Animal Care and Use Committee (IACUC). The Physicians Committee argues that inadequate oversight by the Primate Research Center's IACUC resulted in improper approval and ongoing use of live animals for human nutrition research.

The Physicians Committee requested that APHIS and OLAW investigate the matter and order correction and appropriate penalties.

This is not the Physicians Committee's first allegation of improper animal use by OHSU. In December, the Physicians Committee filed a complaint with the U.S. Department of Agriculture and sponsored billboards near campus urging the administration to stop using live pigs in its general surgery residency program.

Complaint:
https://pcrm.widen.net/s/wvdl5dnzsf/onprc-aphis-and-olaw-complaint_5.2.23

Yours sincerely,
(b) (6)

cc:
Adrian D. Lindsey
Branch Chief, Correspondence Management Division
Office of the Executive Sécretariat
U.S. Department of Agriculture
Whitten Building, (b) (4)
Washington, D.C. 20250
(b) (6)
Adrian.Lindsey@usda.gov, agsec@usda.gov

(b) (6)