AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

Washington, D.C.
1536 16th St. N.W.
Washington, DC 20036
202-483-PETA

Los Angeles
2154 W. Sunset Blvd.
Los Angeles, CA 90026
323-644-PETA

Norfolk
501 Front St.
Norfolk, VA 23510
757-622-PETA

Berkeley
2855 Telegraph Ave.
Ste. 301
Berkeley, CA 94705
510-763-PETA

Info@peta.org
PETA.org

February 28, 2020

Shu-Wan Wang, Technical Specialist
Food Registration Section, Food Safety Division
Taiwan Food and Drug Administration
161-2, Kunyang St., Nangang District
Taipei 115-61, Taiwan

Via email: sww123@fda.gov.tw

Dear Ms. Wang,

Thank you in advance for your time. I am writing to you on behalf of People for the Ethical Treatment of Animals (PETA) and our 6.5 million members and supporters worldwide regarding an important issue. **Based on the scientific critiques presented below, we urge the Taiwan Food and Drug Administration (TFDA) to reevaluate its guideline on joint protection health claims for foods and remove the suggestions and acceptance of animal tests.**

Background

The TFDA prepared a draft guideline in 2020 on experiments that applicants need to perform to substantiate health claims for foods for joint protection, specifically from osteoarthritis (OA).[1] In the guideline, TFDA specified that applicants must conduct human or animal tests.

The guideline recommended two types of animal experiments. One model involves injecting enzymes or other chemicals into animals' joints, which functions to digest or otherwise damage their cartilages. The other model involves surgically severing tissues that support the joints, therefore destabilizing them. Per the TFDA guideline, experimenters are to use adult (10 weeks old) male rats who are kept at a regular 12hr-12hr light-dark cycle and at a 23±2 degree Celsius environment; to induce OA, experimenters can use chemical injection such as papain, or surgeries such as anterior cruciate ligament transection (ACLT), medial menisectomy (MMX), destabilization of the medial meniscus (DMM), or any combination of the three surgical procedures, on the right hind joint of the animals; and, at the end of the experiment, all animals are to be starved for 12 hours then killed and dissected.

The functional measurement, known as the incapacitance test, is used to measure the animals' joint pain, an indicator of the severity of OA. The more severe the pain is, the more likely that the animals would want to lift their right hind limb, resulting in differences in weight distribution between their two hind limbs. During this test, pain relief is purposely withheld from the animals, so as not to mask their pain and interfere with the results.

[1] Email from TFDA to PETA. February 5, 2020.

Affiliates:
- PETA Asia
- PETA India
- PETA France
- PETA Australia
- PETA Germany
- PETA Netherlands
- PETA Foundation (U.K.)

In addition to the blatant cruelty associated with these animal tests, below are some of the scientific limitations of these tests as well as troubling issues related to using rats to substantiate human health claims in general.

Scientific Limitations of the Proposed Animal Tests

To date, there are no FDA-approved disease-modifying OA drugs on the market, despite decades of experiments on animals. Clinical trials that were based on successful tests on animals with ACLT, MMX, and DMM have failed repeatedly. For example, rat models of chemical injection showed that zoledronic acid and a matrix metalloproteinase inhibitor were beneficial, and rat models of MMX showed that salmon calcitonin and vitamin D3 were beneficial as well. However, all of these failed in the subsequent clinical trials.[2] Other animal models such as dogs and rabbits with ACLT, mice with DMM, and mice with chemical injection have also failed repeatedly. These failure are due to unrealistic experimental settings and significant species differences in OA pathophysiology.

Unrealistic Experimental Settings

The animals used in OA experiments rarely mimic the clinical population and scenarios. For example, aging is an important factor in OA etiology,[3] however, the animals used in the tests are generally young. TFDA's guideline specifies that rats who are 10 weeks old should be used, but this age correlates to only the teenage age range in humans.[4]

The female sex is another important risk factor of OA and ovarian function plays an important role in OA pathophysiology,[5] yet few OA experiments take this detail into account. Indeed, TFDA's guideline specifies that male rats should be used during the experiments.

The timing of therapy is also problematic. Human patients typically seek treatment after symptom onset, which is often after substantial structural changes and other molecular pathology in the joints.[6] On the contrary, animal experiments use prophylactic approaches, such that the treatments are given at the same time or shortly after the (arbitrary) induction of OA. TFDA's guideline specifies that the test food should be given to animals starting the day after the induction of OA.

These practices on animals make their "diseases" easier to treat and hence overestimate the effectiveness of the treatments. Further, even if TFDA addresses these issues, there is still the underlying problem that animals are not suitable surrogates for human health, making animal experiments poor research methods.

Species Differences in OA Pathophysiology

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[3] Loeser, R. F. (2013). Aging processes and the development of osteoarthritis. *Current opinion in rheumatology*, *25*(1), 108.
[4] Sengupta, P. (2013). The laboratory rat: relating its age with human's. *International journal of preventive medicine*, *4*(6), 624.
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There are numerous species differences that hinder translational OA research. For example, spontaneous OA is said to be "extremely uncommon in rats of all strains."[7] In other words, rats are largely immune to spontaneous OA, which limits the relevance of rat models to only post-traumatic OA. However, rats are quadrupeds and have drastically different biomechanics of joints and movements, and this leads to different patterns of cartilage loading and compensatory gait alterations under OA compared to humans.[8]

More importantly, unlike humans, rodents (and rabbits) can heal their cartilage lesions spontaneously,[9] which confounds evaluation of treatments. This is further complicated by the fact that different OA induction methods in rats elicit different characteristics of joint pain, in terms of types, durations, severity, and more.[10]

It is also important to note that rats are prey animals and have evolved under selection pressure to hide their pain and weakness. Measuring pain in prey animals is generally challenging because of this as well as stress-related analgesia[11] that can occur in laboratory settings, which are often stress-inducing.

Circadian Rhythm and Inflammation

OA is an inflammatory disease. The circadian clock is known to regulate immune functions and inflammatory responses, and the circadian fluctuations in concentrations of immune modulators coincide with cycles of immune system activity to ensure optimal functions such as tissue repair.[12] Circadian rhythm impairment is hypothesized to be one of the mechanisms for aging associated OA,[13] and shift work is an independent risk factor for OA.[14,15]

Rats are nocturnal and their patterns of circadian rhythm and functions are opposite of humans in many aspects. In experimental settings where rats are kept at a regular 12hr-12hr light-dark cycle (as suggested by the TFDA guideline) and experimenters carry out tests during the day time while the animals are supposed to be at rest, rats endure circadian disruption that perturbs a myriad of physiological functions.[16] Not only does this increase stress in animals, it confounds experiments. The results of animal experiments cannot be trusted especially if performed during day time.

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Cold Stress and Inflammation

The temperature of a typical laboratory environment is about 20 to 26 degree Celsius, as recommended by the *Guide for the Care and Use of Laboratory Animals*.[17] The TFDA guideline suggests 23±2 degree Celsius. However, this is considered too cold for rats. Rats need at least 28 degree Celsius (31.5 degree Celsius for mice) for thermoneutrality and they suffer from chronic cold stress in the laboratory environment, which leads to alterations in metabolism, cardiovascular parameters, respiration, immunological function, and much more.[18] Patients with OA have more cold-inducible RNA-binding protein, which is a pro-inflammatory cytokine.[19] This may be why patients with OA are hypersensitive to coldness and experience more pain in colder weather.[20,21] Cold stress therefore affects OA experiments and is one of the many reasons why animal experiments have poor translatability to humans.[22]

A Note on the 3R Principles

The 3R principles have a hierarchy. "Replacement" is the most important, followed by "reduction," and last "refinement." When experimenters follow the 3R principles, they need to focus on replacement first. Considering that human tests are available and accepted by the guideline, it is clear that non-animal research methods are feasible and hence the replacement principle should be followed. Allowing animal testing in this case is in apparent violation of the 3R principles and the Taiwan Animal Protection Act, which clearly states that "[o]ne shall avoid using live animals for scientific application."[23]

Conclusion

Animal tests are not fit for purpose to substantiate human health claims and should not be recommended or accepted by the TFDA guideline. Further, only human tests can be used to substantiate human health claims. The regulatory agencies in the United States, Canada, European Union, and others do not require or recommend animal tests to substantiate human health claims for foods. They don't accept animal test results as standalone evidence either.[24] Given these facts, along with the numerous scientific limitations and cruelty associated with these animal tests, we respectfully urge TFDA to remove the suggestions and acceptance of animal tests from the guideline on joint protection health claims for foods.

You can contact me by e-mail at FrancesC@peta.org. Thank you for your consideration of our request, and I look forward to your response.

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[23] https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=M0060027
[24] Please see "PETA to Taiwan FDA food health claim animal testing" sent to TFDA on April 18, 2018 for details.

Sincerely yours,

Frances Cheng, Ph.D.
Senior Science Adviser, International Laboratory Methods
Laboratory Investigations Department