COMMENTS ON THE PROPOSED PESTICIDE EXPERIMENTAL USE PERMIT APPLICATION: OXITEC LTD., U.S. Environmental Protection Agency Docket ID No. EPA-HQ-OPP-2019-0274-0363

September 19, 2021

Thank you for the opportunity to submit this comment regarding the request by Oxitec Ltd. for an Experimental Use Permit (EUP) application and the release of OX5034 *Aedes aegypti* in the U.S. This comment was written by Julian Morris and is being submitted on behalf of Reason Foundation.

Reason Foundation's nonpartisan public policy research promotes choice, competition and a dynamic market economy as the foundation for human dignity and progress.

Julian Morris has been researching and writing on issues relating to the regulation of biotechnology for over 20 years. He has consistently supported a response that appropriately balances risks and benefits of introducing new technologies—and has opposed arbitrary and capricious restrictions on such technologies. The following is a small selection of his relevant work (including two comments on earlier applications for experimental use permits for Oxitec mosquitoes):

Morris, J. (2019) *Comments on the Proposed Pesticide Experimental Use Permit Application: Oxitec Ltd., U.S. Environmental Protection Agency Docket ID No. EPA-HQ-OPP-2019-0274*, Portland, Oregon: International Center for Law and Economics.

Pusok, K. and Morris, J. (2018) *Comment on Proposed Pesticide Experimental Use Permits*, Los Angeles: Reason Foundation

Morris, J. (2010) "Unprincipled Precaution," *The Wall Street Journal*, 16 March.

Morris, J. (2007) "Precaution, institutions, incentives, heuristics, regulation and hormesis," *Human and Experimental Toxicology*, Vol 26(3), pp. 851-853.

Morris, J. (2002): "The Relationship between Risk Assessment and the Precautionary Principle," *Toxicology*, Vols. 181-182, pp. 127-130.

Morris, J. (2002) "The Precautionary Principle and Biotechnology," *Int. J. Biotechnology*, Vol 4, No. 1, pp. 46-61.

Morris, J. (ed.) (2000): *Rethinking Risk and the Precautionary Principle*, Oxford: Butterworth- Heinemann.

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Morris, J. and Bate, R. (eds.) (1999): *Fearing Food: Risk, Health and the Environment*, Oxford: Butterworth-Heinemann.

This submission focuses on the benefits and costs associated with the issuance of the EUP requested by Oxitec Ltd. to test the OX5034 *Aedes aegypti* mosquitoes in the states of California and Florida, and the possible wider impacts of approving the EUP to evaluate the efficacy of OX5034 mosquitoes as a tool for suppression of wild *Aedes aegypti* mosquito populations.

Aedes aegypti mosquitoes are the leading cause of several deadly diseases, including dengue, yellow fever, chikungunya, and Zika.

Mosquitoes are one of the deadliest animals in the world. By spreading and infecting humans with diseases such as malaria and dengue fever, they cause millions of deaths every year.[1] *Aedes aegypti* is one of the most widespread mosquito species globally and is responsible for numerous serious—and often fatal—viral diseases, including:

- Yellow fever, which is endemic in 47 countries in Africa and Latin America, has a mortality rate for those with severe cases of 20 to 50%. Following the implementation of a global vaccine initiative, which began in 2006, the incidence of yellow fever has declined significantly; however, outbreaks in Brazil and several African countries in the past decade have nonetheless resulted in tens of thousands of deaths.[2]
- Dengue, which is now endemic in more than 141 countries, can cause high fever and in vulnerable people can lead to death.[3] Each year, about 400 million people are infected with dengue and about 60 million show symptoms.[4] Dengue likely kills between 10,000 and 20,000 people every year at a global cost of perhaps $9 billion.[5]
- Chikungunya, which causes fever and debilitating joint pain that can last for months, has been identified in 60 countries in Asia, Africa, Europe and the Americas.[6] Large outbreaks in the past two decades in Asia and the Americas have resulted in at least 200,000 confirmed cases, over 2 million suspected cases, and likely contributed to several hundred deaths.
- Zika, which is known to circulate in Africa, the Americas, Asia and the Pacific, can cause microcephaly and other severe fetal brain defects in the offspring of infected mothers.[7]

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[1] https://www.who.int/neglected_diseases/vector_ecology/mosquito-borne-diseases/en/

[2] http://www.who.int/mediacentre/factsheets/fs100/en/

[3] Shepard DS, Undurraga EA, Halasa YA, Stanaway JD (August 2016). "The global economic burden of dengue: a systematic analysis". *The Lancet. Infectious Diseases*. **16** (8): 935–41; Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012;6:e1760; Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL et.al. The global distribution and burden of dengue. Nature;496:504-507.

[4] Bhatt et al., op cit.

[5] Shepard et al., op cit.

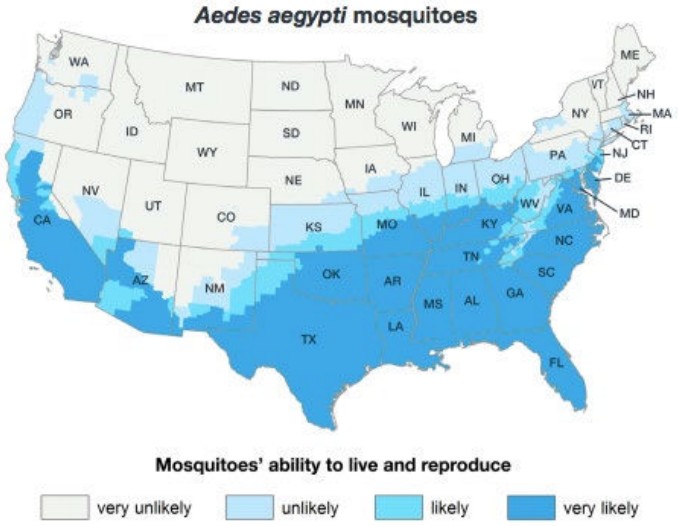
[6] https://www.who.int/en/news-room/fact-sheets/detail/chikungunya

[7] http://www.cdc.gov/media/releases/2016/s0413-zika-microcephaly.html; and http://www.who.int/mediacentre/factsheets/zika/en/

Aedes aegypti mosquitoes spread deadly diseases in the U.S. and in U.S. territories.

While the incidence of mosquito-borne disease in the U.S. is a tiny fraction of what it once was,[8] it remains a threat both in the continental U.S. and in U.S. territories. *Aedes aegypti* is a particular concern. The U.S. Centers for Disease Control (CDC) estimates that *Aedes aegypti's* range extends throughout most of the Southern and eastern U.S. (see Figure 1).

Figure 1: Distribution of *Aedes aegypti* in the United States.



Source: https://www.cdc.gov/zika/pdfs/zika-mosquito-maps.pdf

There have been numerous outbreaks of diseases spread by *Aedes aegypti* in the continental U.S. and in U.S. territories over the past two decades, including:

- Seasonal outbreaks of dengue in the U.S. territories of Puerto Rico, the U.S. Virgin Islands, Samoa and Guam.[9] There was also a dengue outbreak in south Texas in 2005. And there have been frequent cases of local-transmission (albeit in relatively small numbers) in Florida.
- Numerous outbreaks of chikungunya. From 2006 to 2013, an average of 28 people per year in the U.S. tested positive for chikungunya, including locally transmitted cases in Florida, Puerto Rico, and the U.S. Virgin Islands.[10] In 2014, there was a major outbreak in U.S. Territories, leading to at least 4,659 locally-transmitted cases, as well as 12 locally-transmitted cases in Florida.[11] The number of locally-transmitted cases has been falling since then, with 237 reported

[8] https://www.cdc.gov/malaria/about/history/elimination_us.html
[9] https://www.cdc.gov/dengue/epidemiology/index.html
[10] https://www.cdc.gov/chikungunya/geo/united-states.html
[11] https://www.cdc.gov/chikungunya/geo/united-states-2014.html

in 2015,[12] 181 in 2016,[13] 39 in 2017,[14] 8 in 2018,[15] 2 in 2019,[16] and none in 2020 or so-far in 2021.[17] Nonetheless, the potential for future outbreaks remains.

- Sporadic outbreaks of Zika, including in Hawaii, Florida, and Texas, as well as several U.S. territories.[18] In 2017, 433 cases of Zika virus disease cases were reported in the 50 states, including 5 cases acquired through local mosquito-borne transmission in Florida and Texas. In the same year, almost 654 locally-acquired infections occurred in U.S. territories.[19] Since then there have been no reported instances of Zika resulting from local mosquito-borne transmission in the continental U.S. However, there have been nearly 300 cases of locally transmitted Zika in U.S. territories, most of them in Puerto Rico.[20]

The California Department of Public Health recently produced a map showing that *Aedes aegypti* mosquitoes are present in over 20 counties in California, from Shasta in the North to San Diego and Imperial in the South, as can be seen in figure 2.[21]

In the past 20 years, there have been several outbreaks of locally-transmitted dengue in Baja California Sur, Mexico, the most recent being in 2020.[22] Given the prevalence of *Aedes aegypti* (and to a lesser extent *Aedes albopictus*) in California, there is a considerable risk that the disease will spread north and become endemic in the US. Likewise, chikungunya appears to have gained a foothold in Baja California Sur and there is a risk that it, too, could spread north.

Current Aedes aegypti control methods are costly and relatively inefficient.

While an effective vaccine is now available for yellow fever, there are neither vaccines nor effective anti-viral medicines for several of other diseases spread by *Aedes aegypti*, namely dengue, chikungunya and Zika. As a result, the primary means of preventing these diseases is through mosquito control.

Existing mosquito control techniques, including spraying with insecticides and attempting to manage breeding sites (e.g. using larvicides), are costly and often inefficient.[23] For example, the Florida Keys Mosquito Control District spends about $1.1 million per year in the Key West area to achieve an

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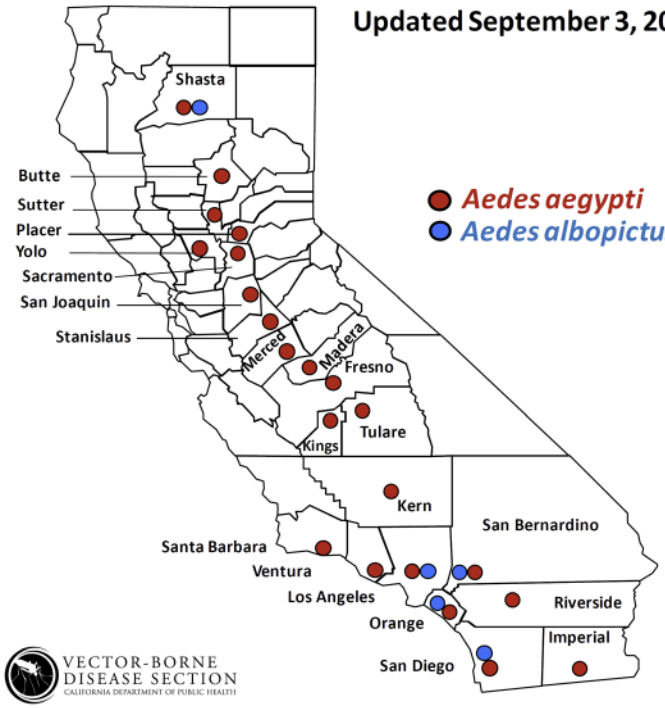
12 https://www.cdc.gov/chikungunya/geo/united-states-2015.html
13 https://www.cdc.gov/chikungunya/geo/united-states-2016.html
14 https://www.cdc.gov/chikungunya/geo/united-states-2017.html
15 https://www.cdc.gov/chikungunya/geo/united-states-2018.html
16 https://www.cdc.gov/chikungunya/geo/united-states-2019.html
17 https://www.cdc.gov/chikungunya/geo/united-states-2020.html; https://www.cdc.gov/chikungunya/geo/united-states-2021.html
18 https://www.cdc.gov/zika/vector/range.html
19 https://www.cdc.gov/zika/reporting/2017-case-counts.html
20 https://www.cdc.gov/zika/reporting/2018-case-counts.html; https://www.cdc.gov/zika/reporting/2019-case-counts.html; https://www.cdc.gov/zika/reporting/2020-case-counts.html; https://www.cdc.gov/zika/reporting/2021-case-counts.html
21 https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/AedesDistributionMap.pdf
22 Vania Serrano-Pinto and Manuel Moreno-Legorretara, "Dengue Hemorrhagic Fever in the Northwest of Mexico: A Two-Decade Analysis," *Revista de Investigacion Clinica*, May-Jun 2017, Vol. 69(3), pp. 152-158. doi: 10.24875/ric.17002101; https://www.iamat.org/country/mexico/risk/dengue
23 Yakob L, Walker T. Alternative vector control methods to manage the Zika virus outbreak: More haste, less speed - Authors' reply. Lancet Global Health. 2016;4(6):e365-6 10.1016/S2214-109X(16)00086-3

estimated 50% reduction of the *Aedes aegypti* population.[24] Moreover, the repeated use of chemical insecticides is leading to rising resistance worldwide, creating challenges for mosquito control programs.[25]

Figure 2: Distribution of *Aedes Aegypti* and *Aedes Albopictus* Mosquitoes in California



Source: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/AedesDistributionMap.pdf

OX5034: technology and potential benefits.

Oxitec has developed OX5034, a strain of the *Aedes aegypti* male mosquito designed to interfere with the natural reproductive cycle of wild *Aedes aegypti*. Male mosquitoes do not bite and so do not spread disease; their sole purpose is to find and mate with female mosquitoes. When OX5034 are released to mate with wild females, the female offspring inherit a self-limiting gene that causes them to die before becoming functional adults. Because male offspring survive, the second generation of males pass on the self-limiting gene. However, in third and subsequent generations, only half the offspring inherit the self-limiting gene; the other half are wild type. As a result, the presence of the self-limiting gene in the population naturally declines to extinction in a few generations.[26]

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[24] http://keysmosquito.org/oxitec-ox513a-trial/

[25] Ranson, H., Burhani, J., Lumjuan, N., & Black IV, W. C. (2010). Insecticide resistance in dengue vectors. TropIKA. net, 1(1), 1-12; Bharati, M. and Saha, D. Multiple insecticide resistance mechanisms in primary dengue vector, Aedes aegypti (Linn.) from dengue endemic districts of sub-Himalayan West Bengal, India. PLoS ONE, September 10,2018. https://doi.org/10.1371/journal.pone.0203207; Amelia-Yap, ZH, Chen, CD, Sofian-Azirun, M, Low VL. Pyrethroid resistance in the dengue vector Aedes aegypti in Southeast Asia: present situation and prospects for management. Parasit Vectors. 2018 Jun 4;11(1):332. https://doi.org/10.1186/s13071-018-2899-0.

[26] https://endmalaria.org/sites/default/files/Enca%20Martin-Rendon.pdf

The self-limiting gene, tTAV (tetracycline repressible transactivator variant), is a gene variant that has been optimized to work only in insect cells. In the wild, offspring that contain the self-limiting gene make a non-toxic protein that ties up the cell's machinery so its other genes are not expressed and the insect dies. The proteins produced are non-toxic in the insects, so if any animals eat them it would be the same as eating a wild insect – they are digested in just the same way that all other insects are digested.[27]

In OX5034, the tTAV gene is *expressed* only in female offspring, through the use of sex-specific alternative splicing. The use of tTAV enables efficient production of OX5034 because the self-limiting gene can be switched off by exposing females to tetracycline.[28] But due to the use of sex-specific alternative splicing, males are not dependent on tetracycline. Indeed, eggs for release have never been exposed to any tetracycline (only the female parents have).

OX5034 also express a gene for fluorescence, enabling more efficient monitoring.[29]

Oxitec's first generation of *Aedes Aegypti* (OX513A) has undergone successful trials since 2009 in several countries (including Brazil, Panama, Malaysia, and the Cayman Islands), establishing the validity of the Oxitec approach: the size of the *Aedes aegypti* population in the targeted areas decreased by more than 90%.[30]

The U.S. Food and Drug Administration (FDA) has already acknowledged the importance and potential benefits of using Oxitec's technology. In 2016, it issued a finding of no significant impact (FONSI) for OX513A.[31]

In May 2020, the EPA granted an EUP for OX5034 in Florida and Texas.[32]

We encourage EPA to take these positive acknowledgments into consideration when deciding on the course of Oxitec's request to undertake further tests of the OX5034 *Aedes aegypti* mosquitoes.

Summary and recommendation.

When evaluating the costs and benefits of issuing an EUP for Oxitec's OX5034 *Aedes aegypti* mosquito, we ask EPA to carefully consider these points:

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[27] https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=vector-control-transmissible-diseases-8245&alias=43534-paho-evaluation-group-meeting-on-aedes-oxitec-534&Itemid=270&lang=en

[28] https://endmalaria.org/sites/default/files/Enca%20Martin-Rendon.pdf

[29] Ibid.

[30] Danilo O. Carvalho et al. "Suppression of a Field Population of Aedes aegypti in Brazil by Sustained Release of Transgenic Male Mosquitoes," *PLoS Neglected Tropical Diseases*, 2015, Vol. 9(7). https://doi.org/10.1371/journal.pntd.0003864 [Brazil]; Renaud Lacroix et al. "Open Field Release of Genetically Engineered Sterile Male *Aedes aegypti* in Malaysia." *PLoS ONE*, 2012, Vol. 7(8): e42771 [Malaysia]; Kevin Gorman et al., 'Short-term suppression of Aedes aegypti using genetic control does not facilitate Aedes albopictus,'" *Pest Management Sciences*, 2016, Vol. 72 (3), pp. 618–628. https://doi.org/10.1002/ps.4151 [Panama]; Angela F. Harris et al., "Successful suppression of a field mosquito population by release of engineered male mosquitoes." *Nature Biotechnology*, 2012, Vol. 30, pp. 828-830. https://doi.org/10.1038/nbt.2350 [Cayman Islands].

[31] https://www.fda.gov/media/96367/download

[32] https://www.epa.gov/pesticides/epa-approves-experimental-use-permit-test-innovative-biopesticide-tool-better-protect

- The burden associated with diseases transmitted by *Aedes aegypti* is very high, including widespread loss of human life. The U.S. is not excluded from this burden.
- The risks of delaying experimental use of OX5034 are potentially enormous. The inefficiency of current mosquito control methods combined with the geographical spread of *Aedes aegypti* means millions of people will continue to get sick unnecessarily if the implementation of more efficient technologies is delayed.
- Oxitec's OX5034 mosquitoes represent significant progress in the control of vector-borne diseases. Successful field trials with Oxitec's first generation tTAV self-limiting mosquito, OX513A, validate the use of this technology. OX5034 offers several additional benefits over the first generation.
- The evidence indicates that there is unlikely to be any significant adverse impact on the environment or human health. To the contrary, the reduction in use of pesticides is likely to benefit the environment, while the greater efficacy and efficiency of this mosquito control method is likely to benefit human health.
- Oxitec has begun field trials with OX5034 in Brazil. Additional field trials, including those proposed in the EUP application will help better evaluate the effects of OX5034 on the environment and human health.
- EPA's EUP approval does not mean that Oxitec's OX5034 mosquitos are approved for commercial use.

Given current inefficient mosquito-control methods, the high burden of vector-borne diseases, and the positive results of previous field trials of the OX5034 *Aedes aegypti* mosquito, Reason Foundation urges the EPA to move forward as quickly as possible in approving Oxitec's request for an EUP to undertake additional field trials in Florida and California. Unfounded fears about this safe technology should not prevent it being implemented as part of the solution to a serious health problem.

Thank you for your time and consideration of these comments.

Sincerely,

Julian Morris

Senior Fellow, Reason Foundation