SAVING THE HORSESHOE CRAB: THE CASE FOR THE OFT-FORGOTTEN, CRITICALLY IMPORTANT LIVING FOSSIL

NOTE

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INTRODUCTION

The humble horseshoe crab is an ancient species. Its direct ancestors roamed the ocean floor some 450 million years ago,[1] and the species has remained evolutionarily stagnant for more than 200 million years.[2] The crab's incredible resilience saw it through many mass extinctions caused by ice ages, asteroid impacts, and climate changes. But today, the existence of this important species is threatened like never before by none other than the *homo sapien*.[3]

Four species of horseshoe crab currently exist, three of which "inhabit the coastal waters of Asia from India to Japan, including the East Indies and Philippines."[4] The last species, the American horseshoe crab, lives along the Atlantic coastline from the Yucatan Peninsula to Maine.[5] Although reliable population data is lacking, some harvest numbers of Asian horseshoe crabs suggest a population drop of 83% over the last five to ten years.[6] If current trends continue, the now endangered Asian species will face extinction. While the plight of the Asian horseshoe crab is dire and its conservation is critical, this note will focus on the status of the American horseshoe crab in the United States.

This note explores the human use of the American horseshoe crab, arguing that such use has put an important species on the road to extinction. This note argues that current conservation efforts are

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[1] D.M. Rudkin & G.M. Young, *Horseshoe Crabs—An Ancient Ancestry Revealed*, *in* BIOLOGY AND CONSERVATION OF HORSESHOE CRABS 25-44 (J.T. Tanacredi et al. eds., 2009).

[2] B. Błażejowski, *The Oldest Species of the Genus*, *in* CHANGING GLOBAL PERSPECTIVES ON HORSESHOE CRAB BIOLOGY, CONSERVATION AND MANAGEMENT 3-14 (R.H. Carmichael et al. eds., 2015). As a result, the horseshoe crab is often referred to as the "living fossil."

[3] The American horseshoe crab is currently considered "vulnerable," the category directly preceding "endangered." D.R. Smith et al., *Limulus Polyphemus*, THE IUCN RED LIST OF THREATENED SPECIES (Oct. 10, 2018), https://www.iucnredlist.org/species/11987/80159830.

[4] D.R. Smith et al., *Conservation Status of the American Horseshoe Crab, (Limulus polyphemus): A Regional Assessment*, 27 REV. FISH BIOLOGY AND FISHERIES 135, 136 (2017).

[5] *Id.*

[6] Glenn Gauvry, *Current Horseshoe Crab Harvesting Practices Cannot Support Global Demand for TAL/LAL: the Pharmaceutical and Medical Device Industries' Role in the Sustainability of Horseshoe Crabs*, *in* CHANGING GLOBAL PERSPECTIVES ON HORSESHOE CRAB BIOLOGY, CONSERVATION AND MANAGEMENT 475, 479-480 (M. L. Botton, et al. eds., 2015). Asian horseshoe crabs are consumed at an alarming rate, and effective conservation is particularly difficult due to the necessary coordination of countries with varying environmental priorities. As a result, little, if any, regulation of Asian horseshoe crab harvesting exists.

insufficient and concludes by proposing a few immediate and forward-looking ways to strengthen them. Part I explains the history of human use of the horseshoe crab and explains the two main uses of the animal today. Part II lays out the modern conservation framework and shows how a key scientific breakthrough can play a role. Part III explains why adoption of this breakthrough has been slow. Part IV proposes some ways to encourage widespread adoption of the new technology. Part V details what can be done today to preserve the horseshoe crab. Finally, Part VI makes some recommendations for future research on this topic.

I. THE IMPORTANCE OF THE HORSESHOE CRAB

A. Historical and Agricultural Use

North Americans have long found uses for the horseshoe crab. Native Americans discovered that the crab's tail made for an effective spearhead and learned that the crab's remains could fertilize their fields.[7] Colonial Americans adopted the latter technique, but also fed horseshoe crabs to their livestock.[8] These practices persisted into the mid-1800s, when harvest increased exponentially.[9] By the early 1960s, population decline, alternative fertilizers, and public health concerns ended previously unsustainable harvesting of the American horseshoe crab.[10] Over the next thirty years, harvesting decreased and populations recovered considerably.[11]

Unfortunately, population recovery did not last. In the early 1990s, use of the horseshoe crab increased again, but this time for a different purpose: bait. Around that time, fishery managers began regulating groundfish.[12] Whelk and eel fishermen, who had previously used those groundfish as bait, sought a substitute to sustain increasing worldwide

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[7] WILLIAM SARGENT, CRAB WARS 67 (2002).

[8] *Id.*

[9] *Id.* "From the 1850s to the 1920s, between 1.5 and two million horseshoe crabs were harvested annually" for these purposes. *Horseshoe Crab*, ATL. STATES MARINE FISHERIES COMM'N, http://www.asmfc.org/species/horseshoe-crab (last visited Dec. 10, 2018).

[10] SARGENT, *supra* note 7, at 68. During the 1960s, horseshoe crab harvest effectively ceased. *Id.*

[11] *Id.* Unfortunately, no specific yearly population estimates exist for years prior to 1998. A lack of such data helped motivate the Atlantic States Marine Fisheries Commission to create a Fisheries Management Plan for the horseshoe crab. Mark L. Botton, *Horseshoe Crabs*, 49 BIOLOGIST 193, 197 (2002). Nevertheless, the significant drop in horseshoe crab harvests during the 1960s would indicate that the population experienced a proportionate rebound.

[12] Jim Berkson & Carl N. Shuster, Jr., *The Horseshoe Crab: The Battle for a True Multiple-Use Resource*, 24 FISHERIES 6, 7 (1999).

demand for their catch.[13] The horseshoe crab, abundant at the time and completely unregulated, seemed perfect.[14]

Fishermen targeted mature female horseshoe crabs.[15] Females are ideal not only because they are larger than males but also because they often bear eggs—an enticing treat for eel.[16] But these females are critical for the species' reproduction, especially since horseshoe crabs can take up to ten years to mature[17] and can be harvested easily with minimal financial expense.[18] Use of the crab as bait grew steadily until 1998, when almost three million crabs were plucked from the Atlantic shoreline.[19]

B. Biomedical Use

While agricultural use of the horseshoe crab ebbed and flowed throughout the nineteenth and twentieth centuries, biomedical researchers studying the crab quietly made breakthrough discoveries. Since the 1930s, scientists have studied and observed the remarkable characteristics of the horseshoe crab's eye.[20] Such research revealed fundamental aspects of visual function universal to humans and many other animals.[21] As the twentieth century progressed, scientists discovered a use for the crab that proved to have much broader implications: endotoxin detection.

Endotoxins are common and dangerous contaminants that exist within the outer membrane of the cell wall of certain bacteria.[22] These organic, nonliving substances are heat-resistant and remain present even after sterilization kills the bacteria that carried them.[23] In fact, endotoxins are released in the greatest quantities when the carrier bacteria are killed.[24]

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[13] *Id*.

[14] *Id*.

[15] Gary Kreamer and Stewart Michels, *History of Horseshoe Crab Harvest on Delaware Bay*, *in* BIOLOGY AND CONSERVATION OF HORSESHOE CRABS 308 (J.T. Tanacredi et al. eds., 2009).

[16] *Id.*

[17] Smith et al., *supra* note 4, at 147.

[18] ATL. STATES MARINE FISHERIES COMM'N, INTERSTATE FISHERY MANAGEMENT PLAN FOR HORSESHOE CRAB (1998).

[19] Only harvest numbers are available; total abundance data was and remains lacking.

[20] M. Errigo et al., *Visually Guided Behavior of Juvenile Horseshoe Crabs*, 201 THE BIOLOGICAL BULL. 271 (2001).

[21] *Id.*

[22] Tom Maloney et al., *Saving the Horseshoe crab: A Synthetic Alternative to Horseshoe Crab Blood for Endotoxin Detection*, 16 PUB. LIBR. OF SCI. BIOLOGY 2 (2018).

[23] Norman Wainright, *Ever Had an Injection? Thank a Horseshoe Crab*, EUREKA (June 17, 2013), eureka.criver.com/ever-had-an-injection-thank-a-horseshoe-crab/.

[24] Kenneth Todar, *Bacterial Endotoxin*, TODAR'S ONLINE TEXTBOOK OF BACTERIOLOGY, textbookofbacteriology.net/endotoxin.html (last visited Oct. 11, 2018); PAUL F. TORRENCE, MOLECULES OF NATURE: BIODIVERSITY, THE SIXTH MASS EXTINCTION AND THE FUTURE 213 (2017).

The resilience, prevalence, and lethality of endotoxins make their detection vital.

From the 1940s until the 1970s, the biomedical industry used the United States Pharmacopeia's ("USP") rabbit test to detect endotoxins.[25] This test involved testing biomedical products destined for humans on large numbers of rabbits first.[26] If the rabbits subsequently showed signs of illness, the sample was deemed contaminated.[27] However, this method was flawed: it was costly, often inaccurate, and criticized by the public for requiring the euthanization of hundreds of thousands of rabbits annually.[28]

The realization that the crab's blood could be used to detect endotoxins was the result of happenstance. Horseshoe crabs are easy-to-capture animals with primitive and uncomplicated biological systems.[29] Scientists often use them to test their theories because the crabs present fewer confounding variables than more complicated specimens.[30] One such scientist was Frederick Bang, who in 1955 tested the crab's immune system by injecting the animals with bacteria.[31] Bang observed that the crab's blood almost immediately "clumped into stringy masses," a reaction that he could replicate even after boiling the bacteria solution.[32] In 1964, Bang and his research partner Jack Levin first described in detail the coagulation in the blood of the *Limulus polyphemus*, or the American horseshoe crab.[33] Intrigued, they continued their research and learned that the presence of endotoxins in the blood triggers coagulation.[34]

These discoveries led to research that uncovered several key insights about the crab's unique immune system and its pale blue blood.[35] First, horseshoe crab blood consists of only one kind of cell, an ovoid amoebocyte.[36] Second, when a crab is injured and bacteria enters its blood, these amoebocyte cells release their contents into the

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25 Carl N. Shuster, Jr. et. al., *Clotting Cells and Limulus Amebocyte Lysate*, in THE AMERICAN HORSESHOE CRAB 310, 314-15 (Carl N. Shuster, Jr. et al. eds., 2003).

26 *Id.*

27 *Id.*

28 Botton, *supra* note 11, at 196; Maloney et al., *supra* note 22, at 2.

29 *Conservation Challenges,* THE HORSESHOE CRAB, http://horseshoecrab.org/conservation/, (last visited Oct. 12, 2018).

30 *Id.*

31 Frederick Bang, *A Bacterial Disease of Limulus Polyphemus*, 98 BULL. JOHNS HOPKINS HOSPITAL 325 (1955).

32 *Id.*

33 Jack Levin & Frederick Bang, *The Role of Endotoxin in the Extracellular Coagulation of Limulus Blood*, 115 BULL. JOHNS HOPKINS HOSPITAL 265 (1964).

34 Jack Levin & Frederick Bang, *Clottable Protein in Limulus: Its Localization and Kinetics of its Coagulation by Endotoxin,* 19 THROMB DIATHES HAEMORRH 186 (1968).

35 Botton, *supra* note 11, at 196

36 *Id.*

environment.[37] The contents of the amoebocyte cells are adhesive and form a durable, visible, gel-like clot.[38] Third, this clotting helps to seal off the wound, preventing excessive blood loss and trapping bacteria within the clot.[39] Fourth, this clotting occurs even in the absence of living bacteria, suggesting a high degree of sensitivity to endotoxins.[40] This string of discoveries led to the creation of *Limulus* amoebocyte lysate ("LAL"), a test for endotoxins.[41]

To produce LAL, horseshoe crabs are first caught and then bled at specialized facilities.[42] The collected blood is then centrifuged to isolate the key amoebocytes.[43] Next, water is added to the amoebocytes, causing them to lyse, or rupture, and release the critical coagulation proteins.[44] The resulting lysate will "produce an instantaneous, visible reaction to endotoxins," if present, upon application to a test subject.[45] If no reaction is observed, then no endotoxins are present and the test subject is ready for use.

After LAL was invented in the late 1960s, the biomedical industry moved to adopt it. In 1969, pathologists James F. Cooper, Henry N. Wagner, and Jack Levin[46] began exploring whether LAL could replace the rabbit test.[47] Two years later, they found that LAL performed at least as well as the rabbit test in detecting endotoxins.[48] 1970 marked the first time LAL was used in the diagnosis of a human disease.[49] In 1971, LAL successfully detected endotoxins in pharmaceutical drugs.[50] By 1973, the Food and Drug Administration ("FDA") took note of LAL.[51] The FDA formally approved of LAL as a substitute for the rabbit test in 1977.[52]

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37 *Id.*

38 *Id.*

39 *Id.*

40 *Id. See also* Maloney et al., *supra* note 22, at 2; Levin & Bang, *supra* note 34.

41 Botton, *supra* note 11, at 196.

42 Jordan Krisfalusi-Gannon et al., *The Role of Horseshoe Crabs in the Biomedical Industry and Recent Trends Impacting Species Sustainability*, 5 FRONTIERS IN MARINE SCIENCE 1, 2 (2018).

43 *Id.*

44 *Id.*

45 *Id.*

46 James Cooper et al., *Quantitative Comparison of In Vitro and In Vivo Methods for the Detection of Endotoxin*, 78 J. LABORATORY AND CLINICAL MED. 138 (1971).

47 *Endotoxin Timeline,* THE HORSESHOE CRAB, http://www.horseshoecrab.org/med/timeline.html (last visited Oct. 12, 2018).

48 James Cooper et al., *supra* note 46.

49 Jack Levin et al., *Detection of Endotoxin in Human Blood and Demonstration of an Inhibitor*, 75 J. LABORATORY AND CLINICAL MED. 903 (1970).

50 James Cooper et al., *The Limulus Test for Endotoxin (Pyrogen) in Radiopharmaceuticals and Biologicals*, 26 BULL PARENTERAL DRUG ASS'N 153 (1972).

51 Status of Biological Substances Used for Detecting Bacterial Endotoxins, 38 Fed. Reg. 1404 (Jan. 12, 1973).

52 Licensing of Limulus Amebocyte Lysate, 42 Fed. Reg. 57749 (Nov. 4, 1977).

LAL developed into one of the most important substances in the biomedical industry. With an incredible ability to positively detect endotoxins at a concentration of one part per trillion, LAL is currently the worldwide standard for endotoxin detection.[53] Glenn Gauvry, a horseshoe crab conservationist, has noted that "[f]ew people understand how deeply the [LAL] industry affects the lives of nearly every man, woman, child and domestic animal in the world, who are dependent upon medical service for their health."[54] The vast majority of vaccines, medicines, and devices that will come in contact with the cardiovascular system of a living animal are tested by LAL.

But the process of harvesting LAL from horseshoe crabs has a serious impact on the species' wellbeing and survival. Despite the intention to return bled horseshoe crabs alive but dazed to their natural habitat, many are harmed in the process.[55] The ASMFC estimates that 15% of horseshoe crabs die as a result of biomedical bleeding.[56] However, some studies have observed average mortality rates of up to 30%.[57] These studies require that the test subjects be held in captivity for a time to measure their mortality rates, thereby introducing a level of experimental bias that the LAL industry attacks.[58] Ultimately, the true mortality rate subsequent to bleeding is unknown. Nevertheless, other studies observed that bleeding has more serious effects on females. In waters that are only open to biomedical harvest, such as Massachusetts' Pleasant Bay,[59] the ratio of males to females is drastically larger than in other nearby areas. Furthermore, a post-bleed female mortality rate of 30% has been observed in Pleasant Bay, substantially higher than the 15% previously assumed.[60] Although the true cause of this mortality rate is also unknown, Leschen and Correia posit a plausible theory:[61] if egg production in female crabs is as energy intensive as it is in many other species, and since most harvest occurs during spawning season, then "this investment

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53 TORRENCE, *supra* note 24, at 214.

54 Gauvry, *supra* note 6, at 477.

55 Maloney et al., *supra* note 22, at 4.

56 ATL. STATES MARINE FISHERIES COMM'N, 2013 HORSESHOE CRAB STOCK ASSESSMENT UPDATE 3 (2013).

57 Thomas J. Novitsky, *Biomedical Implications for Managing the Limulus polyphemus Harvest Along the Northeast Coast of the United States*, *in* CHANGING GLOBAL PERSPECTIVES ON HORSESHOE CRAB BIOLOGY, CONSERVATION AND MANAGEMENT 483, 487 (R.H. Carmichael et al. eds., 2015).

58 *Id.*

59 MASS. DIVISION OF MARINE FISHERIES, MASSACHUSETTS 2009 COMPLIANCE REPORT TO THE ATLANTIC STATES MARINE FISHERIES COMMISSION – HORSESHOE CRAB 7 (2009).

60 *Id.*

61 A.S. Leschen & S.J. Correia, *Mortality in Female Horseshoe Crabs (Limulus polyphemus) from Biomedical Bleeding and Handling: Implications for Fisheries Management*, 43 MARINE AND FRESHWATER BEHAVIOUR AND PHYSIOLOGY 135 (2010).

of energy prior to the spawning season could render females more physiologically stressed or depleted than males by the bleeding process."[62]

Those crabs that do survive the bleeding process most likely fail to replenish those lost to the process and the bait industry. During breeding season, horseshoe crabs move to small, sandy beaches on the banks of estuaries that connect to the Atlantic Ocean.[63] While the crabs lay and fertilize their eggs in these shallow waters, they are easily harvested.[64] Females are preferred by the biomedical industry since they are larger and have more blood to give.[65] Those females that do survive the bleeding process often show reduced spawning activity,[66] and some fail to spawn at all.[67] Males also have exhibited noticeably lethargic behavior, indicating an even lower chance of successful breeding, following the bleeding process.[68]

All signs indicate a growing global demand for endotoxin detection methodologies. As the global population inflates and life expectancies lengthen, human demand for these methodologies will increase.[69] Furthermore, despite a lack of definitive data, the Asian horseshoe crab's population is "by all accounts . . . diminishing," and the crab is considered endangered in Japan, Taiwan, China, Hong Kong and Singapore.[70] Although some promising synthetic substitutes for LAL exist, the biomedical industry has been slow to transition.[71] If these trends continue, the American horseshoe crab's population will suffer due to the global demand for LAL. This shift in demand could occur as soon as 2026.[72]

II. CONSERVATION

Today's regulatory mechanisms are overseen by a variety of governmental entities. In the United States, individual states retain the

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62 *Id.* at 138.

63 Novitsky, *supra* note 57, at 487; *see also* Botton, *supra* note 11, at 197.

64 Novitsky, *supra* note 57, at 487.

65 *Id.* at 491.

66 Leschen & Correia, *supra* note 61, at 138.

67 R.L. Anderson et al., *Sublethal Behavioral and Physiological Effects of the Biomedical Bleeding Process on the American Horseshoe Crab, Limulus Polyphemus*, 225 THE BIOLOGICAL BULL. 137 (2013).

68 *Id.*

69 *Id.*

70 *Id.* at 479-80.

71 Maloney et al., *supra* note 22, at 10. Reasons for the delay are explained in more detail below.

72 *The Horseshoe Crab*, REVIVE AND RESTORE, https://reviverestore.org/horseshoe-crab/ (last accessed June 3, 2019).

authority to regulate the marine fisheries within their jurisdiction.[73] Marine fisheries in federal waters are regulated by the National Marine Fisheries Service ("NMFS").[74] State regulators often act in a coordinated fashion through the Atlantic States Marine Fisheries Commission ("ASMFC"), an interstate fisheries management organization made up of representatives of each state on the Atlantic coast.[75] The ASMFC, working closely with the NMFS and the U.S. Fish and Wildlife Service ("FWS"), strives to maintain healthy coastal fisheries through the implementation of fishery management plans.[76] Federal law provides that any state included within such a plan must implement its conservation provisions; noncompliant states face a moratorium on the relevant fishery.[77] However, states are free to establish whatever regulations they please on subjects that the ASMFC is silent on.[78] Since the horseshoe crab is not currently listed as threatened or endangered by the FWS, it is not protected by the Endangered Species Act ("ESA").[79]

In the late 1990s, state and federal fishery managers struggled to set sustainable harvesting caps due to a lack of hard data regarding the number of crabs caught and the size of the population.[80] To make matters worse, the ASMFC had not yet addressed the topic of horseshoe crabs, resulting in harvest regulations that varied wildly across the Atlantic states from stringent in states like New Jersey and Delaware to nonexistent in Connecticut and Maine.[81] More than half of the Atlantic states had either very lax or no regulations at all.[82]

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[73] Botton, *supra* note 11, at 196.

[74] *About Us*, NOAA FISHERIES, https://www.fisheries.noaa.gov/about-us (last accessed Oct. 20, 2018).

[75] SARGENT, *supra* note 7, at 82.

[76] *About Us*, ATLANTIC STATES MARINE FISHERIES COMMISSION, http://www.asmfc.org/about-us/program-overview (last accessed Oct. 20, 2018).

[77] Atlantic Coastal Fisheries Cooperative Management Act, 16 U.S.C § 5106 (1993); *see also id.*

[78] SARGENT, *supra* note 7, at 82.

[79] *See Environmental Conservation Online System*, U.S. FISH AND WILDLIFE SERV., https://ecos.fws.gov/ecp/ (follow "All Threatened and Endangered Animals" hyperlink; then note the lack of a listing for *Limulus polyphemus*) (last visited Nov 12, 2018). Notably, however, the International Union for Conservation of Nature and Natural Resources (IUCN) lists the American horseshoe crab as "vulnerable" to local extinction with the extent and degree of the risk varying by region. *See* Smith et al., *supra* note 3. Also, the Migratory Bird Treaty Act, 16 U.S.C. §§ 703–712 (1918), could conserve the horseshoe crab's habitat while also preserving the red knot's critical feeding grounds.

[80] Botton, *supra* note 11, at 197.

[81] ATL. STATES MARINE FISHERIES COMM'N, *supra* note 18, at 7-8. New Jersey restricts the harvesting season, permits harvest only by hand, requires a horseshoe crab permit, and mandates monthly reporting. Delaware's regulations are similarly stringent.

[82] *Id.*

A. Modern Regulation

In 1996, nearly one hundred fishery managers, conservation advocates, LAL producers, and others met at a conference at the University of Delaware to consider conservation of the horseshoe crab. They were brought there by a mutual desire to, among other things, "develop consensus on the status of the horseshoe crab[;] . . . determine information needs to better manage the resource[;] . . . and build partnerships among resource agencies, research institutions, industry, and environmental groups."[83] Conference attendees discussed the need for "a coordinated management strategy to eliminate loopholes in the mosaic" of state regulations.[84] These loopholes severely hindered enforcement, since harvesters "could simply catch horseshoe crabs in one of the regulated state's waters and then land their catch in an unregulated port."[85] The discussion also emphasized the importance of the crab not just to humans as bait and for biomedical use, but also for migratory shorebirds, such as the endangered red knot. Red knots depend heavily on the nutrient-rich eggs of the crab in order to refuel and continue their long journey to their breeding grounds in the Arctic, where food is scarce.[86] The red knot is physically unable to rely on any other substitute; its 9,300 mile migration causes its stomach to wither to the point where only easily digestible foods are edible.[87] Thus, the crab found an unlikely ally in so-called "birders," who saw the fate of their beloved red knot inseparably intertwined with the living fossil.

History may well show that the red knot saved the horseshoe crab. In the time immediately following the Delaware convention, shorebird conservationist organizations such as the National Audubon Society and the American Bird Conservancy implored the ASMFC to protect the crab. But they did not implement any substantial, harmonious solution.[88] The ASMFC "didn't have the time or money to listen to a bunch of birders."[89] Researcher Bill Sargent once noted that one should "[n]ever underestimate the persistence of birders . . . .They have members, organizations, and e-mail alerts. The commission did not realize any of this. Within weeks they were deluged with petitions, e-mails, even letters

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[83] PROCEEDINGS OF THE HORSESHOE CRAB FORUM: STATUS OF THE RESOURCE 3 (J. Farrell & C. Martin eds., 1997).

[84] Botton, *supra* note 11, at 197.

[85] Sebastian B. Okun, *Mating in the Moonlight: The Battle to Save the American Horseshoe Crab*, 18 OCEAN AND COASTAL L. J. 195, 204 (2012).

[86] Lawrence J. Niles et al., *Navigation Effects of Horseshoe Crab Harvest in Delaware Bay on Red Knots: Are Harvest Restrictions Working?* 59 BIOSCIENCE 153, 154 (2009).

[87] *Id.*

[88] SARGENT, *supra* note 7, at 82.

[89] *Id.*

from Congress."[90] The ASFMC quickly relented. In 1997, the ASMFC authorized a task force to develop a plan to regulate the horseshoe crab fisheries. In 1998, the commission created a management plan in response to the task force's findings.[91] The implementations were designed to augment the medley of existing state regulations and standardize them across the Atlantic seaboard.[92] Carl N. Shuster has remarked that "if it were not for the concern about the fate of the migratory shorebirds that flock to the Delaware Bay area each spring, there probably would not be a coast-wide horseshoe crab management plan today."[93]

The ASMFC's new Horseshoe Crab Fisheries Management Plan ("FMP") strove "to conserve and protect the horseshoe crab resource to maintain sustainable levels of spawning stock biomass to ensure its continued role in the ecology of coastal ecosystems, while providing for continued use over time."[94] The FMP implemented a management program to achieve this end by curtailing overfishing and promoting population growth through conservation and monitoring. To further conservation, the FMP mandated a bait harvest threshold that capped the permissible amount of crabs caught and required states to protect the crab's habitat within their jurisdiction.[95] The FMP required states with existing robust regulations to secure approval by the Horseshoe Crab Management Board before making any changes to their regulations.[96] Other states were required to implement management measures and protect the crab's habitat within their jurisdiction.[97] To improve monitoring, the FMP required that a comprehensive and standardized monitoring plan be "instituted throughout the Atlantic Coast."[98] This plan hoped to address concerns raised by the task force that the crab's population trends "are poorly understood due to the limited amount of information" currently available.[99] Monitoring efforts were standardized across ASMFC member states and mandated data collection on such subjects as crab density, post-bleed mortality rates, and habitat.[100] Other

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90 *Id.*

91 ATL. STATES MARINE FISHERIES COMM'N, *supra* note 18, at 1.

92 *Id.* at 7-9, 25.

93 Carl Shuster, *Horseshoe Crab Conservation: A Coast-Wide Management Plan*, *in* THE AMERICAN HORSESHOE CRAB 367 (Shuster et al., eds., 2003).

94 ATL. STATES MARINE FISHERIES COMM'N, *supra* note 18, at iii.

95 *Id*. at 26.

96 *Id.*

97 *Id.* at 25.

98 *Id*. at iv.

99 *Id.* at 4.

100 ATL. STATES MARINE FISHERIES COMM'N, *supra* note 18, at 4.

measures were aimed at conserving and restoring habitat[101] and enforcing compliance.[102]

Since the ASMFC implemented the FMP in 1998, it has been amended seven times in order to respond to changing population dynamics.[103] Addendum I, implemented in 2000, set a state-by-state annual quota of horseshoe crab landings.[104] The addendum also recommended that the NMFS protect a critical breeding ground in federal waters at the mouth of the Delaware Bay.[105] The following year, the NMFS created the Carl N. Shuster Horseshoe Crab Reserve (Shuster Reserve). Bait fishing is banned in the Reserve, but some licensed biomedical harvesting is permitted.[106] Addendum II, approved in 2001, "establish[ed] criteria for voluntary quota transfers between states."[107] Addendum III (2004) imposed "additional restrictions on the bait harvest of horseshoe crabs of Delaware Bay-origin and expanded the biomedical monitoring requirements."[108] Addendum IV (2004) strengthened Addendum III's harvest restrictions and set them to expire in 2006.[109] Addenda V (2008) and VI (2010) further extended Addendum III's restrictions until they expired in 2013.[110] Finally, Addendum VII established an Adaptive Resource Management (ARM) framework, which directs that future regulations should take into account the populations of both red knots and horseshoe crabs.[111] The framework considers the needs of the red knot "to determine optimal horseshoe crab harvest" and shapes ongoing initiatives and assessments to protect both species.[112]

B. The Failures of Modern Regulation

Today, protections for the horseshoe crab seem robust. Some states, like New Jersey, ban bait harvesting entirely.[113] Bait harvest across the

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101 *Id.* at 27.

102 *Id.* at 31.

103 Krisfalusi-Gannon, *supra* note 42, at 8.

104 ATL. STATES MARINE FISHERIES COMM'N, ADDENDUM VII TO THE INTERSTATE FISHERY MANAGEMENT PLAN FOR HORSESHOE CRAB FOR PUBLIC COMMENT 1 (2012). A "landing" refers to the process of catching and harvesting a horseshoe crab.

105 ATL. STATES MARINE FISHERIES COMM'N, ADDENDUM I TO THE INTERSTATE FISHERY MANAGEMENT PLAN FOR HORSESHOE CRAB 5 (2000). There, it was recommended that no harvesting of horseshoe crabs, for any purpose, should be permitted.

106 Smith et al., *supra* note 4, at 162. The reserve is named after a researcher who devoted his life's work to preserving the horseshoe crab.

107 ATL. STATES MARINE FISHERIES COMM'N, *supra* note 104, at 1.

108 *Id.*

109 *Id.*

110 *Id.* Upon expiration, the FMP reverted back to the Addendum III requirements.

111 Krisfalusi-Gannon, *supra* note 42, at 8.

112 *Id.*

113 N.J.S.A. 23:2B-21 (2008).

Atlantic seaboard has decreased significantly, from over 2.5 million crabs harvested in 1999 to about 1 million crabs in 2017.[114] Some areas, such as Delaware Bay and the Carolinas, have demonstrated steady or slowly increasing population growth.[115] However, other areas, such as New England, continue to suffer from population declines.[116] These results show that current regulatory controls are insufficient. There are two reasons why.

First, the ASMFC's most recent Addendum no longer focuses on the horseshoe crab alone. Instead, management goals are now tied to the viability of other species, such as the red knot.[117] This is concerning because the new methodology involves determining and enforcing a maximum sustainable harvest, which is not an effective management strategy for the long term. While conservation of red knots is also important, Addendum VII shows that the migratory shorebird is beginning to take precedence over the very animal that the FMP was designed to protect. Consequently, most data regarding the crab focuses on crabs harvested rather than crabs left in the ocean.[118] This may ultimately harm the marine animal because the interests of the two species are not always aligned. For example, red knot conservationists prefer to see spawning surveys to learn how many eggs may be available for the red knot's stopover. On the other hand, crab enthusiasts are more interested in trawling surveys that better estimate the animal's abundance. A better strategy would focus on preserving "a critical threshold of horseshoe crab abundance that provides sufficient eggs" for red knots.[119]

Second, although crab fishery regulations have been reconsidered and reworked many times throughout the last twenty years, biomedical harvest has been restricted only once and never banned.[120] For example, the original FMP exempted biomedical harvest from restrictions and only asked that states require biomedical companies to report catch data.[121] In

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[114] *Horseshoe Crab*, ATLANTIC STATES MARINE FISHERIES COMMISSION, http://www.asmfc.org/species/horseshoe-crab (last accessed Nov. 4 2018).

[115] Smith et al., *supra* note 4, at 156.

[116] *Id.*

[117] ATL. STATES MARINE FISHERIES COMM'N, *supra* note 104.

[118] Two researchers lamented that "[t]here is currently a lack of abundance information for effectively managing horseshoe crabs *Limulus* polyphemus." David Hata & Jim Berkson, *Factors Affecting Horseshoe Crab Limulus polyphemus Trawl Survey Design*, 133 TRANSACTIONS OF THE AM. FISHERIES SOC'Y 292, 292 (2004). Another agreed. Smith et al., *Abundance of Adult Horseshoe Crabs (Limulus polylphemus) in Delaware Bay Estimated from a Bay-Wide Mark-Recapture Study*, 104 FISHERIES BULL. 456, 461 (2006).

[119] Smith et al., *supra* note 118, at 456.

[120] Up to 10,000 crabs a year may be harvested for biomedical purposes from the Carl N. Shuster Horseshoe Crab Reserve. Smith et al., *supra* note 4, at 162.

[121] ATL. STATES MARINE FISHERIES COMM'N, *supra* note 18, at 26.

2004, the ASMFC expanded reporting requirements for biomedical harvest, but failed to restrict it.[122] Not even the Shuster Reserve is a proper sanctuary, since some biomedical harvest is allowed.[123] There is no definitive explanation for the consistent and apparent hole in conservation measures. Perhaps the laxness is explained by the importance of the crab to the health and safety of most people around the world. Or maybe the loophole is justified by the nonlethal intent behind the bleeding process. Regardless, substantial evidence shows that the biomedical industry's continued use of LAL is preventing the crab's full and speedy recovery.

Biomedical harvest is one of the largest manmade threats to the horseshoe crab today. Current regulations have reduced bait harvest substantially, but the continued neglect of biomedical harvest is increasingly concerning. In 1998, the ASMFC established a mortality ceiling of 15% for bled and returned crabs.[124] This ceiling was only followed until 2006; in every year thereafter, the biomedical industry exceeded this ceiling without penalty.[125] Furthermore, biomedical harvest "is significant and increasing."[126] It is true that current regulations have modestly reversed population reductions in areas such as South Carolina, where one LAL producer is located.[127] But populations are only stable in Delaware, Maryland, and Virginia, where four other producers are located, and they are declining in Massachusetts and Rhode Island, where one producer is headquartered.[128] In 2017, over 500,000 crabs were harvested for LAL production—a 285% increase from 1989.[129] The rising biomedical harvest magnifies lethal and sublethal effects to the point of materially affecting horseshoe crab populations.

But the exact degree to which rising biomedical harvest hinders recovery is difficult to ascertain. Although coast-wide biomedical harvest is reported to the ASMFC, region-specific data is not publicly available due to confidentiality agreements.[130] The lack of public data "prevents accounting for mortality due to biomedical activity in regional

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122 ATL. STATES MARINE FISHERIES COMM'N, ADDENDUM III TO THE INTERSTATE FISHERY MANAGEMENT PLAN FOR HORSESHOE CRAB (2004).

123 Smith et al., *supra* note 4, at 162.

124 Novitsky, *supra* note 57, at 488.

125 *Id.*; *see also* Smith et al., *supra* note 4, at 152.

126 *Id.* at 151.

127 Smith et al., *supra* note 4, at 165.

128 *Id.*

129 ATL. STATES MARINE FISHERIES COMM'N, 2018 REVIEW OF THE ATLANTIC STATES MARINE FISHERIES COMMISSION FISHERY MANAGEMENT PLAN FOR HORSESHOE CRAB (LIMULUS POLYPHEMUS) (2018).

130 Smith et al., *supra* note 4, at 152.

assessments and harvest management."[131] Novitzky asserts that secret reporting cannot be justified: "Open reporting needs to be applied to the biomedical industry. If small commercial fishermen and bait dealers are required to report their catches, sex ratios, and other information, there can be no valid reason for biomedical manufacturers to be exempt from full disclosure."[132] He goes on to argue that the bait industry as a whole is substantially smaller by revenue as compared to the biomedical industry, so biomedical companies cannot reasonably claim confidentiality due to company size.[133]

III. A NEW ERA OF ENDOTOXIN TESTING?

A. Recombinant Factor C

For decades, LAL was the only viable test for endotoxins. But there is now another way, discovered by biologists 9,000 miles away from where the horseshoe crab's blood was first studied.[134] Recombinant Factor C has existed as an alternative to LAL for fifteen years. However, for reasons discussed below, biomedical companies are still wary of using it.

Singaporean molecular biologists Jeak Ling Ding and Bow Ho, unable to afford the LAL they needed to assist a local hospital, set out to create a less expensive substitute.[135] Scientists had previously identified Factor C as the specific molecule within the crab's blood that detects bacterial toxins,[136] and biotechnology at the time was making great strides in the study of recombinant DNA ("rDNA"),[137] which is genetically engineered DNA that has been duplicated within a host cell.[138] rDNA can be put to

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131 *Id.*

132 Novitsky, *supra* note 57, at 497.

133 *Id.*

134 Sarah Zhang, *The Last Days of the Blue-Blood Harvest*, THE ATLANTIC (May 9, 2018), https://www.theatlantic.com/science/archive/2018/05/blood-in-the-water/559229/.

135 *Id.*

136 Sadaaki Iwanaga et al., *The Hemolyph Coagulation System in Invertebrate Animals*, 5 J. OF PROTEIN CHEMISTRY 255 (1986).

137 Zhang, *supra* note 134.

138 Suliman Khan et al., *Role of Recombinant DNA Technology to Improve Life*, 2016 INT'L J. OF GENOMICS 1 (2016). To create rDNA, a certain gene of interest is first identified within a strand of DNA from a donor organism's cells. Next, the gene is separated from the DNA strand. Then, the gene is introduced into the DNA of a plasmid, which is a genetic structure in a cell. Splicing the gene into the DNA of a plasmid is necessary to allow the gene to replicate within a cell as part of the plasmid; without the plasmid, the gene would be destroyed. Thereafter, the gene-containing-plasmid is placed within a host cell that will replicate itself, including the gene-containing plasmid. A.J.F. GRIFFITHS ET AL., AN INTRODUCTION TO GENETIC ANALYSIS (7th. ed. 2000). During this process, the gene, which is a set of instructions for a cell, directs the bacterium to, for example, create a substance. Finally, the substance is harvested from the host cell, is purified, and is ready for use. *How Did They Make Insulin from Recombinant DNA?*, NAT'L LIB. OF MED.,

many different uses, from creating bacteria with certain desired traits to causing host bacteria to create a certain substance. rDNA is used to synthetically create human insulin,[139] and Ding and Ho used the same process to create their own recombinant Factor C ("rFC") from the horseshoe crab gene responsible for its production.[140] When announcing their discovery, Ding and Ho expressed reserved excitement that "recombinant Factor C may [be a] substitute [for] conventional 'LAL' . . . in the near future."[141]

By many accounts, rFC is a superior test to LAL. Although the testing process differs slightly,[142] a review of ten recent studies examining the efficacy of rFC shows that it is as effective as or better than LAL at detecting endotoxins.[143] And since rFC contains one active compound that only detects the presence of endotoxins, the test is not susceptible to the false positives that sometimes occur when LAL is used.[144] One study also found that "rFC overcame other sources of unreliable results occurring during LAL testing [that] include inhibitory constituents of the sample; fewer invalid results, which necessitate re-testing; [and] less interference in complex samples."[145]

B. rFC: A good idea?

rFC is not without its critics. Among rFC's most vocal opponents is Charles River Laboratories, a key producer of LAL, which has published many articles cautioning against rFC.[146] Charles River warns that (1) rFC

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https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-interactive/recombinant-DNA/recombinant-dna-technology-alternative.html (last visited Oct. 20, 2018).

139 *Id.* Insulin was previously sourced from animals. *See* B. Richter & G. Neises, '*Human' Insulin Versus Animal Insulin in People with Diabetes Mellitus*, 2005 COCHRANE DATABASE OF SYSTEMATIC REV. 1 (2005).

140 Jeak Ding & Bow Ho, *A New Era in Pyrogen Testing*, 19 TRENDS IN BIOTECHNOLOGY 277, 278 (2001).

141 Wang et al., *Functional Expression of Full Length Limulus Factor C in stably Transformed Sf9 Cells*, 23 BIOTECHNOLOGY LETTERS 71, 76 (2001).

142 Instead of creating a visible clot, rFC illuminates the test subject if it is contaminated. So, the fluorescence is first tested before the introduction of the test subject, and then tested again after the introduction of the test subject. The difference in the level of fluorescence signifies the amount of endotoxins present. *See* Jeak Ding & Bow Ho, *Endotoxin Detection – from Limulus Amebocyte Lysate to Recombinant Factor C*, *in* 53 ENDOTOXINS: STRUCTURE, FUNCTION AND RECOGNITION. SUBCELLULAR BIOCHEMISTRY 187 (X. Wang & P. Quinn eds., 2010); *see also* Maloney et al., *supra* note 22, at 5.

143 Maloney et al., *supra* note 22, at 5-6.

144 *Id.* at 5.

145 *Id.* at 7-8 (citing Holger Grallert et al., *EndoLISA®: A Novel and Reliable Method for Endotoxin Detection*, 8 NATURE METHODS 884 (2011)).

146 *See e.g.*, John Dubczak, *Standing Guard*, PDA LETTER, https://www.pda.org/pda-letter-portal/archives/full-article/standing-guard (last accessed Nov. 20, 2018); *see also Recombinant*

production is not regulated;[147] (2) rFC has not yet been sufficiently scrutinized;[148] (3) rFC is not as accurate as LAL;[149] and (4) biomedical harvest is necessary for conservation regulations to stand.[150] None of these points survive scrutiny.

First, Charles River is keen to point out that rFC manufacturers are not regulated by the FDA. While this is true,[151] such regulation is unnecessary. rFC is essentially a quality control test. Other such tests, such as those for pH, clarity, or residual solvents, are not regulated by the FDA.[152] Ultimately, the FDA is only concerned about the level of endotoxins in a certain drug or substance.[153] If a drug manufacturer uses some alternative to LAL and achieves the mandated purity, the FDA is indifferent so long as the alternative appears in USP standards or is otherwise independently validated.[154]

Second, Charles River argues that rFC has not been sufficiently scrutinized. The company often notes the fifteen-year wait between the discovery and FDA approval of LAL, highlighting the large number of side-by-side efficacy tests that were performed.[155] This may be Charles River's strongest argument, to the extent that it favors strenuous testing for a new endotoxin detection standard. However, it is quickly weakening. Fifteen years have already passed between the discovery of rFC and the present day.[156] In that time, at least ten studies have confirmed the efficacy of rFC,[157] and the FDA has accepted rFC as an alternative test to LAL.[158] rFC has undergone enough scrutiny to show promise. Although more testing may be warranted, rFC should be adopted in the near future.

Third, Charles River asserts that rFC is less effective than LAL. To bolster its point, the company proffers a white paper comparing different

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Factor C Under the Microscope, EUREKA, http://eureka.criver.com/recombinant-Factor-c-under-the-microscope/ (last accessed Nov. 20, 2018).

147 *Recombinant Factor C*, *supra* note 146.

148 *Id.*

149 Dubczak, *supra* note 146.

150 Wainright, *supra* note 23.

151 Telephone Interview with Robert J. Meyer, Principal, Greenleaf Health (Nov. 21, 2018); DEBORAH CRAMER, THE NARROW EDGE: A TINY BIRD, AN ANCIENT CRAB, AND AN EPIC JOURNEY 117-118 (2015). This point is explored in more detail below.

152 CRAMER, *supra* note 151, at 118.

153 Meyer, *supra* note 151.

154 *Id.*; *see also* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, PYROGEN AND ENDOTOXINS TESTING: QUESTIONS AND ANSWERS (2012). More on the dynamic between the FDA and USP is discussed below.

155 Dubczak, *supra* note 146; *see also Recombinant Factor C*, *supra* note 146.

156 Maloney et al., *supra* note 22, at 6.

157 *See id.*

158 FOOD & DRUG ADMIN., *supra* note 154.

rFC and LAL tests.[159] However, the paper's key evidence does not support Charles River's claim. First, Charles River underscores that rFC correlated with LAL only 94.4% of the time.[160] But the white paper itself observed "[n]o significant deviation in results" between the rFC tests and the LAL tests, and it concluded that the tests produced "comparable" results.[161] Second, even if that 5.6% deviation were significant, it is likely due to some combination of formulation differences between the various tests and the susceptibility of LAL to false positives. Moreover, this argument crumbles in the face of the many other studies demonstrating that rFC is at least as effective as—if not more effective than—LAL.[162] In fact, I could not find a single study showing that rFC is *less* effective than LAL.

Finally, Charles River emphasizes that LAL production is necessary for the continued conservation of the horseshoe crab. The company goes as far as saying that the ASMFC's management plan was motivated by a desire to maintain a steady supply of crabs for LAL production; without biomedical bleeding, the crab would be doomed.[163] This argument is based on a flawed premise. As Section II.A of this paper shows, the ASMFC's plan was primarily motivated by birders who were concerned that an irreplaceable food source for their beloved endangered bird would soon be gone. Even if 100% of endotoxin testing was conducted using rFC, conservation regulations would remain in full effect for the benefit of the red knot and the environment in which the horseshoe crab lives.

C. Regulatory Hurdles Thwart rFC Adoption

Unfortunately, the new era has been slow in coming. Although rFC has been commercially available since 2003,[164] biomedical companies have been hesitant to adopt it for several reasons. First, "manufacturers and regulators have been justifiably cautious in the adoption of new detection technologies" for a health matter as serious as endotoxins.[165] Second, until recently rFC was protected by patent, causing biomedical companies to

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159 *Whitepaper: Detection of Naturally Occurring Bacterial Endotoxins in Water Samples*, EUR. PHARMACEUTICAL REV. (Dec. 23, 2014), https://www.europeanpharmaceuticalreview.com/whitepaper/29826/whitepaper-detection-of-naturally-occurring-bacterial-endotoxins-in-water-samples/. Ironically, this paper supports the use of rFC as a substitute for LAL.

160 Dubczak, *supra* note 146.

161 *Whitepaper*, *supra* note 159.

162 *See, e.g.*, *id.*

163 Wainright, *supra* note 23.

164 Maloney et al., *supra* note 22, at 6.

165 *Id.*

worry about relying on a sole supplier for such a critical test.[166] Third, endotoxin testing is heavily regulated, and rFC is not yet endorsed by the USP. Circumventing this regulatory roadblock to use rFC is a burdensome process because of the complex relationship between the FDA and the USP.

The USP is an independent, not-for-profit, nongovernmental pharmacopeia that predates the FDA by more than 85 years.[167] The standards-setting organization was created to remedy a "lack of uniformity in medical practices."[168] Today, the USP is recognized as an "official compendium" under the Food, Drug, and Cosmetic Act ("FDCA").[169] This means that the FDA is required by law to enforce any standards set by the USP as a baseline.[170] Although the FDA may not contradict the USP, it may choose to strengthen or compliment the USP's standards.[171]

The USP maintains a Bacterial Endotoxins Test ("BET") in Chapter 85 of its compendia.[172] Chapter 85 currently designates LAL as the sole approved test for endotoxin detection; rFC is notably absent.[173] In fact, rFC lacked any regulatory approval at all until 2012, when the FDA approved rFC as an alternative to LAL.[174] However, the agency conditioned its use on an expensive validation process.[175] The high cost of transitioning to rFC is magnified by the requirement that each unique product tested with rFC be individually validated.[176] Consequently, only one drug to date has exclusively relied on rFC for endotoxin testing.[177]

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166 *Id.* at 10; *see also* Zhang, *supra* note 134.

167 United States Pharmacopoeia, *USP Timeline*, http://www.usp.org/about/usp-timeline (last accessed Nov. 20, 2018).

168 *Id.*

169 21 U.S.C. § 321(j) (1938).

170 *See generally* 21 U.S.C. § 301 *et. seq.*; Meyer, *supra* note 151.

171 M3yer, *supra* note 151; *see also* FOOD & DRUG ADMIN., *supra* note 154.

172 *<85> Bacterial Endotoxins Test*, UNITED STATES PHARMACOPOEIA, http://www.usp.org/harmonization-standards/pdg/general-methods/bacterial-endotoxins (last accessed Nov. 20, 2018); Interview with Gregory Amidon, Research Professor of Pharmaceutical Sciences, University of Michigan (Nov. 21, 2018).

173 FOOD & DRUG ADMIN., *supra* note 154.

174 *Id.* at 5.

175 *Id*.

176 *Recombinant Factor C Assay*, LONZA, https://bioscience.lonza.com/lonza_bs/NL/en/recombinant-Factor-c-assay (last accessed Nov. 22, 2018).

177 *FDA Approves First Drug Using the Recombinant Factor C Assay for Endotoxin Testing*, LONZA, (Nov. 8, 2018), https://www.lonza.com/about-lonza/media-center/news/Tensid/2018-11-08-14-00-English.aspx.

IV. WAYS TO CATALYZE CHANGE

Although current biomedical and ecological measures are insufficient for the long-term preservation of the animal, a sufficient shift to rFC may still occur in time to save this important species. This section explores two ways to realize that shift. Section IV.A offers a two-stage plan to eliminate the need for the validation of rFC as applied to each unique drug. Section IV.B proposes listing the crab as threatened or endangered under the ESA.

A. Include rFC in the USP's Bacterial Endotoxin Test Standard

The simplest way to effect meaningful positive change for the horseshoe crab would be for the USP to include rFC into its BET standard. Doing so would alleviate the need for pharmaceutical companies to independently verify each individual drug they wish to test with rFC.[178] Unfortunately, the simplest conceivable solution is a difficult one to achieve; the USP is a conservative organization with an immensely important mission, so it is likely that the USP will not move quickly enough on its own. Nevertheless, a path to progress can still be forged. I propose a plan consisting of two sequential stages that, upon their completion, should lead to the adoption of rFC into the USP's BET standard. First, biomedical harvesting of the crab should be further restricted. Second, a pre-competitive consortium of major industry players should be formed for the purpose of extensively validating rFC.

1. Amend the ASMFC's horseshoe crab FMP to further restrict biomedical harvest and return the conservation focus to the horseshoe crab.

Section II.A of this paper discussed the various conservation measures in place today to protect the horseshoe crab. Although apparently robust, the latest addendum to the horseshoe crab's FMP dilutes the conservation focus away from the animal that the FMP was designed to protect. Moreover, closer scrutiny shows that the vast majority of regulations are only relevant to bait harvest. Even in places where bait harvest is heavily restricted or banned outright, biomedical harvest is freely permitted.

Restricting biomedical harvest further would benefit both short-term and long-term conservation. In the short term, fewer crabs would be subjected to the bleeding process, leading to less lethargy and more reproduction. In the long term, the decreased supply of crabs would lead to an increase in the price of LAL relative to rFC, incentivizing greater

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[178] FOOD & DRUG ADMIN., *supra* note 154.

adoption of the relatively cheaper synthetic test. An acceptable alternative to stronger yearlong harvest restrictions would be a complete ban on harvesting during the crab's breeding months.[179] Such a restriction should be part of a new addendum that returns the conservation focus to the crab itself.

A more expensive supply of LAL is critical to the success of the second step. Should LAL become expensive enough, biomedical companies would be stuck between a rock and a hard place. They must either absorb the increased cost of LAL and continue to use it, or transition to rFC and pay for expensive validation time after time. However, there is a way out of this quandary: a pre-competitive consortium.

2. Join major biomedical companies in a pre-competitive consortium to validate rFC for acceptance by the USP.

A pre-competitive consortium is a concerted effort among competitors aimed at improving noncompetitive aspects of their business.[180] These consortia focus on "non-product specific research tools or data with the goal of benefitting the entire industry rather than a single firm."[181] Pre-competitive collaboration offers the benefits attendant with resource pooling, knowledge pooling, and intellectual property pooling while attempting to set industry standards or solve common problems.[182]

Pre-competitive consortia are particularly common in the biomedical industry, where the realities of the industry have turned competitors into collaborators.[183] Total spending on biomedical research in the United States topped $100 billion in 2007,[184] and research and development costs to produce one drug are estimated at $1.8 billion or more.[185] Despite this immense investment, the industry was unable to produce proportionate results.[186] This discrepancy is substantially due to the large amount of duplicative research and trial and error methods on the part of industry players acting independently.[187] Although common practice in the past, independent, secretive research is no longer efficient or sustainable;

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179 This idea was first proposed by Novitsky, *supra* note 57.

180 MARGIE PATLAK ET AL., EXTENDING THE SPECTRUM OF PRE-COMPETITIVE COLLABORATION IN ONCOLOGY RESEARCH 60-65 (2010).

181 Jorge Contreras & Liza Vertinsky, *Pre-Competition*, 95 N.C. L. REV. 67, 70 (2016).

182 *Id.*

183 *Id.* at 71.

184 E. Ray Dorsey et al., *Funding of US Biomedical Research, 2003-2008*, 303 J. AM. MED. ASS'N 303, 137 (2010).

185 Jill S. Altshuler et al., *Opening Up to Pre-competitive Collaboration*, 2 SCI. TRANSLATIONAL MED. 52cm26, 1 (2010).

186 *Id.*

187 *Id.*

historical data shows that the "number of new FDA approved drugs per billion dollars of R&D spending roughly halved every nine years between 1950 and 2010."[188]

By the early 2000s, the FDA was fielding criticism that it was both stifling innovation and not encouraging it enough.[189] In response, the FDA launched its Critical Path Initiative ("CPI") in 2004.[190] The CPI was conceived to improve research and development processes by facilitating collaborative research and the adoption of scientific innovations.[191] The FDA hoped that this modernization effort would help it better carry out its dual roles as protector and promoter of the public health. Since the CPI was introduced, several consortia have formed.[192]

The CPI was one of the FDA's first major attempts to generate pre-competitive collaboration among biomedical companies. Another similar initiative, broader and larger than the CPI, was introduced in 2011.[193] The first of this initiative's eight goals is to "modernize toxicology to enhance product safety."[194] In furtherance of this goal, the FDA planned to conduct independent and collaborative research into "new measurement technologies" of toxicity levels in biomedical products.[195] The scope of such research should include the study of rFC.

Although these types of consortia implicate antitrust law, there generally should not be an antitrust problem. For its part, the FDA not only tolerates but encourages legitimate pre-competitive activity on the theory that such activity benefits the entire industry rather than any specific firm.[196] Furthermore, "legitimate collaborative R&D agreements have long been recognized by courts and antitrust enforcement agencies as offering significant procompetitive benefits."[197] As long as these consortia are truly pre-competitive and not a restraint on trade, courts and regulators will appreciate their ability to "spread the financial burden of costly research, to combine technical skill and knowledge to promote greater innovation, to accelerate the development of new products, and to lower research and production costs through economies of scale, thereby

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188 Contreras & Vertinsky, *supra* note 181, at 75.

189 Janet Woodcock & Raymond Woosley, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 ANN. REV. MED. 1, 2 (2008).

190 *Id.*

191 *Id.*

192 *Id.* at 8.

193 FOOD & DRUG ADMIN., ADVANCING REGULATORY SCIENCE AT FDA (2011).

194 *Id.* at 3.

195 *Id.* at 7.

196 Contreras & Vertinsky, *supra* note 181, at 71.

197 *Id.* at 102.

increasing overall social welfare."[198] Most legitimate pre-competitive consortia will be upheld under the common law antitrust rule of reason.[199]

After the biomedical harvest of the horseshoe crab is restricted and the price of LAL increases, biomedical companies should collaborate with the FDA to hasten the full validation of rFC in a way satisfactory to the USP. This sort of pre-competitive activity fits neatly into the FDA's mission to promote the public health through scientific innovation. Biomedical companies would be financially incentivized to invest in this undertaking, which would be encouraged under one of the FDA's several modernization initiatives, and the FDA would be a happy partner in this effort. The findings of this consortium should be submitted to the USP for approval so that it might include rFC in its BET standard.

B. List the American Horseshoe Crab as Threatened or Endangered under the ESA

Forming a pre-competitive consortium to hasten USP approval of rFC is viable in the short term. In the long term, though, another avenue may be more effective: the ESA. Currently, the American horseshoe crab is not protected under the ESA, and it is unlikely to be immediately eligible.[200] Section IV.B.1 lays out the framework of the ESA. Section IV.B.2 explains the crab's current conservation status and explores potential reasons why the ESA fails to protect it. Section IV.B.3 predicts the implications of listing the crab as threatened or endangered under the act.

1. Framework of the Endangered Species Act

The ESA[201] aims "to conserve to the extent practicable the various species of fish and wildlife facing extinction . . . ."[202] The main federal agencies that administer the Act are the FWS and the NMFS.[203] The FWS

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198 *Id.*

199 *Id.*

200 *Species Search Results*, U.S. FISH & WILDLIFE SERVICE, https://ecos.fws.gov/ecp0/pub/SpeciesReport.do?groups=J&listingType=L&mapstatus=1 (last visited Nov. 24, 2018). However, the animal is currently listed as "vulnerable" under the IUCN Red List. Smith et al., *supra* note 3. In the IUCN's hierarchy of classifications, "vulnerable" means vulnerable to extinction. The classification lies in between "near threatened" and "endangered."

201 16 U.S.C. §§ 1531-1544 (1973).

202 *Id.* § 1531(a)(4).

203 *Summary of the Endangered Species Act*, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY https://www.epa.gov/laws-regulations/summary-endangered-species-act (last accessed Dec. 5, 2018).

maintains a list of threatened and endangered species that are protected by the various provisions of the ESA.[204]

Among these protections is a ban on the taking of any endangered species.[205] Under the ESA, harming, hunting, pursuing, killing, trapping, capturing, collecting, or attempting any of the aforementioned acts is considered an illegal taking.[206] Protections exist for threatened species too, but to a lesser extent. Under the ESA, the Secretary of the FWS may promulgate protective regulations of threatened species as "necessary and advisable to provide for the conservation of such species."[207] The Secretary may exercise this power to prohibit any act with respect to threatened species that would be prohibited by the ESA against endangered species.[208] So while threatened species are not explicitly protected by the Act, the Secretary may enact his or her own protections up to but not exceeding those applicable to endangered species.

Violators of the ESA are subject to civil and criminal penalties.[209] Those who knowingly violate the protective provisions or regulations promulgated under the ESA are subject to a civil penalty consisting of a fine of up to $51,302[210] for each individual violation.[211] Those same persons whose violation involves interstate or foreign commerce are subject to criminal penalties of up to $50,000, up to 1 year in prison, or both.[212]

2. The Current Conservation Status of the Horseshoe Crab and Its Status under the ESA

Of the imperiled species lists currently in existence, the International Union for Conservation of Nature ("IUCN") Red List and the ESA's threatened and endangered species list are among the most influential. The Red List is the most widely used imperiled species list in the world.[213] The ESA, while smaller in scope, "is arguably the world's most effective

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204 *Id.*

205 16 USCS § 1538(a)(1)(B) (1973).

206 *Id.* § 1532(19).

207 16 U.S.C. § 1533(d) (1973).

208 *Id.*

209 *Id.* § 1540.

210 In accordance with the Federal Civil Penalties Inflation Adjustment Act Improvements Act of 2015, Pub. L. No. 114-74, § 701, 129 Stat. 599 (2015) (codified in a note following 28 U.S.C. 2461), the FWS now adjusts its civil fines yearly for inflation. $51,302 is the current fine for a knowing violation of § 1538. *See* Fish and Wildlife Service Civil Penalties; 2018 Inflation Adjustments for Civil Monetary Penalties, 83 Fed. Reg. 5950 (Feb. 12, 2018).

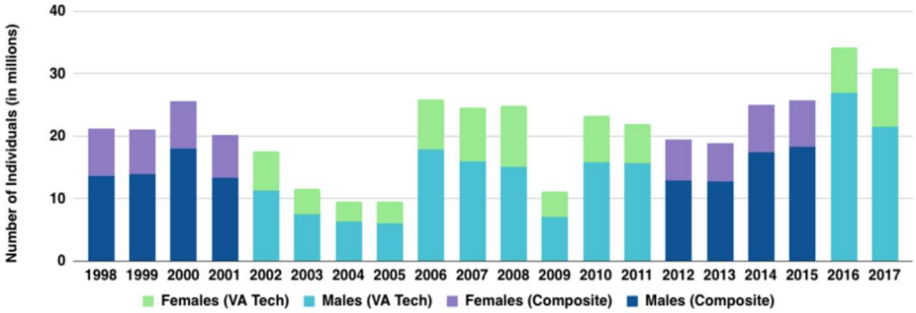
211 16 U.S.C. § 1540(a).

212 *Id.* § 1540(b).

213 J. Berton C. Harris et al., *Conserving Imperiled Species: a Comparison of the IUCN Red List and U.S. Endangered Species Act*, 5 CONSERVATION LEVELS 64, 64 (2011).

biodiversity protection law."[214] A key difference between these lists is the presence of a regulatory apparatus to enforce listings. The IUCN lacks such an apparatus, while the ESA is backed by the power of the U.S. government.

Unfortunately, the horseshoe crab's current conservation status is not entirely clear. Historically, most statistics focused on landings, not abundance, which made effective conservation something of a guessing game.[215] Today's data is not much better. Virginia Tech conducts a scientifically validated trawl survey to determine the abundance of horseshoe crabs in the Delaware Bay region.[216] This survey is the preferred method to determine abundance in the region, and is the only continuing survey across the Atlantic seaboard focused on abundance.[217] From 2012 until 2015, the survey failed to achieve full funding, so suboptimal data was used instead.[218] Abundance data region shows that population levels are unpredictable, but stable. Currently, ongoing and reliable abundance data is limited only to the Delaware Bay region.



Estimated Population of Mature & Newly Mature Horseshoe Crabs in the Delaware Bay Region by Year[219]

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214 *Id.* at 65.

215 Hata & Berkson, *supra* note 118, at 292; *see also* Smith et al., *supra* note 118, at 461.

216 *Horseshoe Crab Trawl Survey Provides Critical Data*, VIRGINIA TECH DEPARTMENT OF FISH AND WILDLIFE CONSERVATION, https://www.fishwild.vt.edu/temp/horseshoe_crab.html (last visited Dec. 1, 2018).

217 *The Horseshoe Crab: A Keystone Species*, DELAWARE DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENTAL CONTROL, https://perspectives.dnrec.delaware.gov/stories/s/The-Horseshoe-Crab-A-Keystone-Species/v3f5-m3tj/ (last visited Dec. 1, 2018).

218 *Id.* This data was "determined using a composite index . . . created from the DNREC Division of Fish & Wildlife's Delaware Bay Trawl Survey and New Jersey Department of Environmental Protection's Delaware Bay and Atlantic Ocean trawl surveys." *Id.*

219 Image available at *The Horseshoe Crab: A Keystone Species*, *supra* note 217.

The lack of continuing, reliable abundance data outside of the Delaware Bay region is the biggest obstacle to listing the crab as threatened or endangered under the ESA. Without such data for all Atlantic seaboard regions, gaining ESA protections may prove exceedingly difficult. For this reason, it is imperative that abundance surveys be expanded across the Atlantic seaboard. Doing so is not cost prohibitive; the survey operated by Virginia Tech, for example, is relatively inexpensive.[220] The challenge may lie in finding funding; Congress discontinued federal funding for Virginia Tech's survey in 2014 and is unlikely to fund other surveys.[221]

Notwithstanding the lack of specific data, the IUCN has listed the American horseshoe crab as "vulnerable," similar to the "threatened" category under the ESA.[222] In doing so, the IUCN relied on the same data sets that the ASMFC used in its 2013 Horseshoe Crab Stock Assessment Update.[223] Both the ASMFC and the IUCN analyzed the data sets and came to the same conclusion: horseshoe crab abundance has increased slightly in the Southeastern region (North Carolina through Florida) and remained stable in the Delaware Bay region, but has decreased in New York and the New England region.[224] Since the crab is in danger of local extinction in some areas, the IUCN lists it as vulnerable.[225]

The difference between the IUCN's listing and the lack thereof under the ESA could have many explanations. First, not enough specific data currently exists to justify a listing under the ESA. The ASMFC admits that "[t]he status of the stock is unknown largely due to the lack of long-term data sets for commercial landings and stock abundance."[226] The data is probably insufficient because few studies are specifically designed to monitor horseshoe crab populations; most data is collected as a secondary effort.[227] Second, the FWS is careful when listing new species because of the consequences a listing brings. Since the Act legally protects species,

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220 The total cost of the survey is $200,000. 2015 MARYLAND FMP REPORT, (AUGUST 2016) SECTION 12. HORSESHOE CRAB (LIMULUS POLYPHEMUS), MD. DEPARTMENT OF NATURAL RESOURCES (2016).

221 *Id.*

222 Smith et al., *supra* note 3.

223 *Id.* at 157. The data came primarily from benthic trawls but also came from seines and spawning surveys.

224 *Id.* at 166; *Horseshoe Crab*, *supra* note 114.

225 Smith et al., *supra* note 4, at 135.

226 *Horseshoe Crab*, *supra* note 114.

227 Smith et al., *supra* note 4, at 157. Only one benthic trawl is specifically designed to monitor horseshoe crab populations. Spawning surveys were also designed with horseshoe crabs in mind, but trawling is generally the preferred method for measuring abundance. https://perspectives.dnrec.delaware.gov/stories/s/The-Horseshoe-Crab-A-Keystone-Species/v3f5-m3tj/.

a new listing involves imposing significant cost and responsibility on government agencies.[228] Listings are often opposed because they can have "profound economic consequences" by stopping land development that will impact an imperiled species.[229] The IUCN may feel freer to list species since doing so is not as consequential. Third, the FWS may be inadequately funded, so it is simply incapable of listing every imperiled species.[230] As a result, the agency focuses on severely imperiled species first, a category to which the horseshoe crab does not yet belong.[231] Fourth, there is evidence that the FWS primarily lists species after being heavily pressured by citizen petitions and lawsuits.[232] Such "[p]etitions and/or lawsuits were involved with 71% of listings from 1974 to 2003 and have become even more important in recent years."[233] Finally, it is possible that the FWS is willing to "accept a higher risk of extinction compared to the IUCN."[234]

Given the serious and strict consequences of an ESA listing discussed in the following section, the crab is unlikely to be protected in the near future. As previously mentioned, though, global demand for endotoxin detection methodologies will only rise as the global population grows and lives longer. Conservation measures have only been able to stabilize horseshoe crab populations, despite being in place for twenty years. If comprehensive, dedicated, and consistent trawling surveys collect data showing a decreasing population trend in an area, an ESA listing for the horseshoe crab may become warranted. Should that day come, the crab could still be saved by such a listing.

3. Implications of Listing the Horseshoe Crab as Threatened or Endangered

If FWS listed the horseshoe crab as a threatened or endangered species under the ESA, bait fisherman and LAL producers would be forced to abandon their use of the horseshoe crab because they would be unable to obtain permits to continue harvesting the crab. Ordinarily, the Secretary of the FWS may issue permits that allow for persons to engage in acts otherwise prohibited by the ESA.[235] Such permits include permits for

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228 Harris, *supra* note 213, at 7.

229 *Id.*

230 *Id.* at 2.

231 *Id.* at 4.

232 *Id.*

233 *Id.* at 5. In fact, it appears that the FWS is so burdened with citizen petitions and lawsuits that it struggles to act on its own listing priorities. *Id.*

234 Harris, *supra* note 213, at 5.

235 16 U.S.C. § 1539 (1973).

takings that serve scientific purposes (Scientific Permits),[236] permits for small takings that serve larger conservation goals (Conservation Permits),[237] and permits for takings if they are "incidental to, and not the purpose of, the carrying out of an otherwise lawful activity" (Incidental Take Permit).[238]

But none of these permits are available to bait fishermen. These fishermen are clearly ineligible for Scientific Permits; their use is commercial, not scientific. They are not eligible for Conservation Permits either, as bait-related takings are large and serve no conservation purpose. Bait fishermen are also ineligible for Incidental Take Permits, since the very purpose of their activity is to take crabs. Nevertheless, the whelk and eel fisheries that rely on horseshoe crab bait are not out of luck. Scientists at the University of Delaware developed an artificial bait that substantially reduces the amount of horseshoe crab necessary to attract whelk and eel.[239] This artificial bait reduces the amount of crab necessary to equip a whelk and eel pot from one crab to one-sixteenth of one crab while remaining just as effective as traditional bait.[240] It also has the added benefits of being cheaper to purchase and easier to store than traditional bait.[241] Although the artificial bait does require the use of some amount of horseshoe crab, the 93.4% reduction in the amount of crab used will likely suffice to grant artificial bait manufacturers a Conservation Permit. These manufacturers would satisfy both requirements for a Conservation Permit. First, the magnitude of their taking is relatively small. Second, their taking is for a conservation purpose because the absence of a substitute for traditional bait would incentivize fishermen to violate the ESA. Since fishermen could just catch and immediately process horseshoe crabs aboard their boats where detection is unlikely, the availability of an alternative bait which is cheap and easy to use would eliminate the incentive to break the law.

No permits are available to the biomedical companies that create LAL, either. These companies are not eligible for a Scientific Permit. Although the taking of the crabs is indeed for a scientific purpose, a Scientific

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236 *Id.* § 1539(a)(1)(A).

237 *Id.*

238 *Id.* § 1539(a)(1)(B).

239 Teresa Messmore & Joanna Wilson, *New artificial bait from project funded by DNREC could reduce number of horseshoe crabs used to catch eel and whelk*, STATE OF DELAWARE, http://www.dnrec.delaware.gov/News/Pages/New-artificial-bait-could-reduce-number-of-horseshoe-crabs-used-to-catch-eel-and-whelk.aspx (last visited Dec. 5, 2018).

240 *Id.*

241 Molly Murray, *Team whips up formula to save horseshoe crabs*, USA TODAY (Jun. 3, 2013, 4:47 PM), https://www.usatoday.com/story/news/nation/2013/06/03/environment-horseshoe-crab-bait/2385117/.

Permit may only be issued if the permitted action "will not operate to the disadvantage of such endangered species" and will be consistent with the conservation policy behind the ESA.[242] As discussed in Section II.A, the biomedical bleeding process disadvantages the horseshoe crab by causing death in up to 30% of bled crabs and by causing lethargy that leads to a failure of crabs to breed. Conservation Permits are not available either. Finally, the Incidental Take Permit certainly will not be issued to biomedical companies because these companies intend to take crabs; their takings would not be incidental to the carrying out of an otherwise unlawful activity. Consequently, production of LAL would cease. Nevertheless, the biomedical industry would not be grievously injured by this sudden drought of LAL. After all, rFC already exists, and has been proven to be a cost effective and efficacious solution. Notice that the American horseshoe crab is about to be protected under the ESA would simply motivate the industry to switch to rFC and validate each application while lobbying the USP to include rFC in its official volumes.

In the future, some other threatened or endangered species may be discovered to be a vital component of a cure for some devastating disease. If no synthetic substitute existed, one might worry how the ESA would balance the competing concerns of conservation and human health. This is a legitimate concern, but it is easily dismissed. The policy behind the ESA is to conserve those species facing extinction "to the extent practicable."[243] Surely, if rFC were never discovered, or if another threatened or endangered species were an irreplaceable part of a life-saving drug, conserving those species would not be considered practicable under the Act. Furthermore, although this specific scenario has never before arisen, it is difficult to conceive that a court would uphold the listing of a species under the ESA if the alternative was substantial loss of human life.

Ultimately, listing the horseshoe crab as "threatened" or "endangered" under the ESA would eliminate the traditional use of the crab as bait and the market for LAL. This is an extreme but not a tragic result. Those fisheries that currently rely on the horseshoe crab as bait have a viable and sustainable alternative, and the vacuum created by the loss of LAL would immediately catalyze the adoption of rFC worldwide. More research should certainly be conducted to continue to verify the efficacy of rFC beyond any practicable doubt. However, continuing that research is not mutually exclusive with listing the horseshoe crab as "threatened"

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242 16 U.S.C. § 1539(d).
243 *Id.* § 1531(a)(4).

or "endangered" under the ESA. Doing so would eliminate the threat to the crab by prohibiting both biomedical harvesting and bait harvesting.

V. HOW TO SAVE THE HORSESHOE CRAB TODAY: REPLACE, REDUCE, REFINE

Although the inclusion of rFC into the USP's standards is critical, users of the horseshoe crab can take steps now to prevent any further population decline by implementing the 3Rs. The 3Rs (replace, reduce, and refine) are "guiding principles underpinning the humane use of animals in scientific research."[244] To abide by these guidelines means first showing that there is no reasonable alternative to animal use, and then following each "R." To "replace" means replacing "the use of animals with alternative techniques, or avoid[ing] the use of animals altogether.[245] To "reduce" means reducing "the number of animals used to a minimum."[246] To "refine" means refining the way animals are treated, including "better housing and improvements to procedures which minimize pain and suffering and/or improve animal welfare."[247]

Each of these principles can be applied to human use of the horseshoe crab. First, biomedical users can *replace* LAL with rFC by transitioning today to the synthetic substitute for all endotoxin testing except for final batch testing. Second, biomedical users and bait users can *reduce* their use of the horseshoe crab by committing to adopt best practices in LAL use and transitioning to synthetic bait, respectively. Third, biomedical users can *refine* the way crabs are treated by demanding best practices by LAL producers.

According to industry experts, biomedical users could achieve a 90% reduction in LAL use by replacing LAL with rFC up until final batch testing.[248] When manufacturing drugs, companies must test all inputs and processing materials, such as pharmaceutical grade water, for endotoxins in addition to the final product.[249] However, "[t]here is a regulatory distinction between in-line processing and the final testing of the marketable drug product."[250] This distinction gives most manufacturers the choice to switch to rFC for almost all endotoxin testing without any need for action on the part of the FDA or USP; the regulators would find

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244 *The 3Rs and Animal Welfare*, UNDERSTANDING ANIMAL RESEARCH (Feb. 22, 2018, 3:38 PM), http://www.understandinganimalresearch.org.uk/animals/three-rs/.

245 *Id.*

246 *Id.*

247 *Id.*

248 Maloney et al., *supra* note 22, at 10.

249 *Id.*

250 *Id.*

it sufficient that the final product was tested with LAL.[251] Moreover, a significant industry transition to rFC would likely spur the USP to take a more serious look at the synthetic substitute.

Second, biomedical companies can adopt best practices to *reduce* their LAL use. Traditional LAL testing requires multiple preparation steps and "guess and check" methods to complete testing, which consumes a substantial amount of LAL.[252] Today, LAL users can achieve a 95% reduction in their LAL consumption by using specially designed LAL cartridges, which offer the additional advantage of a simpler process and a reduction in human error.[253] Whelk and eel fishermen can also do their part by switching to alternative bait. Alternative bait uses substantially less horseshoe crab material and is cheaper than a whole crab, is easier to store, and can be made by following a simple recipe. States could promote commercial production of alternative bait by offering subsidies to those companies willing to produce it. Furthermore, the ASMFC could promote or even mandate at least partial use of alternative bait.

Finally, biomedical users can *refine* crab treatment to decrease mortality by demanding that their LAL suppliers adopt best practices. For example, producers should keep crabs cool and moist by storing and transporting them in refrigerated containers and covering them with damp cloths.[254] Producers should also mark bled crabs to avoid immediate or later re-bleeding in order to avoid bleeding them to death.[255] Finally, crabs should be returned to the place from which they were harvested within 24 hours.[256] The ASMFC and other regulators could further refinement goals by requiring that producers employ best practices.

While immediate implementation of the 3Rs is important and desirable, it is only a temporary solution. If current trends continue, the Asian horseshoe crab will eventually become extinct. If the USP does not act fast enough and there is insufficient data for an ESA listing, the American horseshoe crab may not be able to avoid extinction even if the 3Rs are followed. So, the 3Rs should be implemented in conjunction with conservation efforts.

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[251] *Id.*

[252] Laura Ann Krause, A Comparative Analysis Between The rFC and LAL Endotoxin Assays for Agricultural Air Samples (2016) (unpublished Ph.D. dissertation, Colorado State University); Wainright, *supra* note 23.

[253] Wainright, *supra* note 23.

[254] *Best Manufacturing Practices*, THE HORSESHOE CRAB, http://www.horseshoecrab.org/med/bestpractices.html (last visited Dec. 5, 2018).

[255] *Id.*

[256] *Id.*

VI. RECOMMENDATION FOR FUTURE RESEARCH

Future researchers looking to delve further into endotoxin detection research should examine the efficacy of another possible alternative to LAL: the Monocyte Activation Test ("MAT"). The MAT is the other alternative that the FDA named in its 2012 guidance document.[257] This test uses a specific blood cell, the monocyte, which is extracted from human blood.[258]

MAT appears to offer several advantages over LAL, and, to some extent, its synthetic brother. Made from either fresh or cryogenically frozen human blood, the test excels at detecting all human-relevant pathogens.[259] LAL and rFC, on the other hand, are restricted to endotoxins.[260] MAT is also able to avoid the false positives that LAL sometimes produces, and is less fickle.[261] The MAT has also already seen some commercial application, and "has been used to reliably resolve discrepancies between LAL results."[262]

However, MAT is not without disadvantages. For one, MAT is dependent on healthy human blood donors and is subject to the same variance errors from which most substances derived from living animals, like LAL, suffer.[263] It also, like LAL, cannot usually detect bacterial toxins on medical surfaces unless specifically optimized to do so.[264] However, such optimization causes the test to take up to 20 hours to complete, making it too time-consuming for regular use.[265]

Some combination of rFC, LAL, and MAT may ultimately be ideal. A paper that examines all three standards, comparing their advantages and disadvantages, would be a productive addition to the academic discourse. That paper should seek to recommend which combination of tests at which stages of drug development would be most effective.

CONCLUSION

All three species of Asian horseshoe crab could be harvested into extinction in as soon as seven years. This will place unknowable pressure on the American horseshoe crab to satiate the world's ever-increasing

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257 FOOD & DRUG ADMIN., *supra* note 154.

258 Krisfalusi-Gannon et al., *supra* note 42, at 8-9.

259 Thomas Hartung, *The Human Whole Blood Pyrogen Test – Lessons Learned in Twenty Years*, 32 ALTERNATIVES TO ANIMAL EXPERIMENTATION 79, 80 (2015).

260 *Id.* at 86.

261 *Id.*

262 Krisfalusi-Gannon et al., *supra* note 42, at 9.

263 rFC is relatively advantageous in that it can be manufactured to avoid this issue.

264 Krisfalusi-Gannon et al., *supra* note 42, at 9.

265 *Id.*

demand for endotoxin tests. The American crab's population is likely to crumble under this pressure.

Regulators realized the crab's impending fate and responded by implementing and repeatedly amending a fishery management plan. However, this plan has been insufficient. Nearly twenty years of regulation has stabilized horseshoe crab populations only in parts of the Atlantic seaboard. And the plan largely fails to impose any restriction on biomedical harvest. Although biomedical bleeding is not intended to be lethal, it nonetheless kills about 30% of crabs. Unknown negative effects also follow bleeding, including lethargy, failure to reproduce, and delayed death.

Thankfully, conservation is still possible. A promising new synthetic substitute, rFC, has existed for many years. Substantial testing of rFC has proven its efficacy relative to LAL. Such testing has also shown that rFC offers several distinct advantages over LAL. rFC is also cheaper to make and use. Despite all of these advantages, rFC has yet to be accepted into the USP's BET standard. This exclusion forces any company that wants to replace LAL with rFC to prove its effectiveness for every unique drug brought to market, which is expensive and burdensome. The added expense and burden have severely dampened the transition to rFC.

There are at least two ways to catalyze this transition. First, the USP can be induced into including rFC into its standard. To accomplish this, the ASMFC should first restrict biomedical harvest. This would increase the price of LAL, thus elevating rFC's relative attractiveness. Next, biomedical companies should form a pre-competitive consortium to facilitate collaboration between companies and with the FDA and validate rFC to a sufficient degree that the USP would accept rFC into its standard.

Second, if enough reliable data is gathered to show severe imperilment, the FWS could list the American horseshoe crab as endangered. This would result in an immediate ban on the vast majority of bait and biomedical harvests. While extreme, this is not a catastrophic outcome. Those who rely on the crab for whelk and eel bait have an effective alternative that uses 94.4% less horseshoe crab material than traditional bait. Producers of the alternative will still be able to harvest a small number of crabs to create the alternative under a Conservation Permit. Biomedical companies would lose access to LAL, but this would only hasten the already initiated transition to rFC.

Further action can be taken today to conserve the horseshoe crab while other long-term efforts progress. First, biomedical users can replace LAL with rFC by transitioning today to the synthetic substitute for all endotoxin testing except for final batch testing. Second, biomedical users

and bait users can reduce their use of the horseshoe crab by committing to adopt best practices in LAL use and transitioning to synthetic bait, respectively. Finally, biomedical users can refine the way crabs are treated by demanding best practices by LAL producers.

The writing is on the wall for the horseshoe crab, and it is up to those who realize that fact to act. If immediate action is taken today and further long-term efforts are implemented, the living fossil will continue to prosper, instead of becoming just another fossil.