Chapter 27
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

Glenn Gauvry

Abstract Globally, injectable pharmaceuticals and parenterals, implantable medical devices and similar therapeutic products are safety tested for endotoxin contamination using indicator reagents derived from the blood of horseshoe crabs. *Tachypleus* and *Limulus* Amoebocyte Lysate (TAL and LAL, respectively) are used in quality control laboratories for testing of raw materials, intermediates and final products to protect public health. As the demand for human and animal drugs and devices increases, so does the demand for TAL and LAL. In the United States, the harvesting of horseshoe crabs (*Limulus polyphemus*) is regulated and monitored. Harvesting limits have been exceeded in recent years and may lead to enforcement of harvesting limits to the American LAL industry. Throughout most of Asia, the harvesting of horseshoe crabs is poorly regulated and unmonitored. All indicators point to a declining population. If the *Tachypleus* population cannot support TAL production for the Asia and Pacific pharmaceutical and medical device industries, companies will entirely depend on LAL for testing. The already limited LAL supply is not sufficient to support this increased global demand and will likely result in increased cost and constrain the availability of pharmaceutical and medical device products. As consumers of horseshoe crab-based products, the pharmaceutical and medical device industries can act to help protect horseshoe crab species and, in turn, protect the long-term availability of endotoxin testing products. Global supply chain initiatives that integrate social and environmental considerations into the qualification and choice of vendors, use of best practices for TAL and LAL production, and developing alternative testing methods will promote a more sustainable TAL/LAL industry that can include reduction of animal-based testing and global conservation of horseshoe crab species.

G. Gauvry (✉)
Ecological Research & Development Group Inc.,
190 Main Street, Little Creek, Dover, DE 19901, USA
e-mail: kabutogani@comcast.net

R.H. Carmichael et al. (eds.), *Changing Global Perspectives on Horseshoe Crab Biology, Conservation and Management*, DOI 10.1007/978-3-319-19542-1_27

Keywords Endotoxin detection • LAL/TAL • Conservation • Pharmaceuticals • Parenterals • Vaccines • Healthcare • Biomedical harvest • Protecting health

27.1 Introduction

The healthcare industry, specifically the manufacturers and users of endotoxin detection products derived from horseshoe crabs, are in a unique position to affect the sustainability of horseshoe crabs as a natural resource that is in decline throughout much of Asia and only marginally stable along the Atlantic coast of the United States, where *Limulus* amoebocyte lysate (LAL) is derived (Fig. 27.1).

The horseshoe crab species are slow to mature and suffer high mortality during growth to adulthood. Horseshoe crabs take 10–12 years to reach maturity. During early developmental years, the juveniles are predated upon by a host of marine creatures. Only 3 out of 100,000 survive their first year (Botton et al. 2003; Carmichael et al. 2003).

Once they reach adulthood, horseshoe crabs have few predators other than humans. If not harvested for bait, human consumption, scientific research or biomedical bleeding, horseshoe crabs are expected to live 10 years or more after reaching maturity (Ropes 1961; Botton and Ropes 1988). It is only when they become adults that they begin their annual spring migration from the shelter of deeper waters to their spawning beaches. Adult horseshoe crabs annually congregate on spawning beaches where females burrow into the sand and lay masses of eggs, which are then fertilized by the males around her. Females lay as many as 25 egg clusters each year or around 100,000 eggs (Shuster and Botton 1985; Leschen et al. 2006). It is during spawning when horseshoe crabs are most vulnerable to harvest for TAL/LAL, bait for several different fisheries, human consumption and folk remedies in certain parts

Fig. 27.1 Geographic ranges of *Carcinoscorpius rotundicauda* (*green*), *Tachypleus tridentatus* (*orange*), *Tachypleus gigas* (*blue*), and *Limulus polyphemus* (*red*)

of the world. It is this often unregulated harvesting pressure, coupled with loss of habitat, which poses the greatest threat to the future survival of these remarkable animals.

The Ecological Research & Development Group (ERDG) a nonprofit organization founded in 1995, whose mission is the conservation of the world's four horseshoe crab species, has partnered with members of the endotoxin detection industry with the belief that the industry, and their customers, have the potential to make a significant difference in the conservation of the world's four horseshoe crab species in ways not possible through traditional conservation strategies. Presently, the growth of the global healthcare industry is entirely dependent upon the harvest and collection of blood from live horseshoe crabs to produce TAL/LAL. Although direct mortality of horseshoe crabs due to LAL production is estimated to be relatively low, 8–15 % (Rudloe 1983; Walls and Berkson 2003), the mortality associated with TAL production is 100 % because after bleeding, the animals are sold to secondary markets for food and chitin production. The survival of this biomedical industry is dependent on the survival of three of the world's four horseshoe crabs species. Hence, any factors that affect horseshoe crab survival, even those external to the industry, have potential to affect the sustainability of the industry, giving industry members a unique motivation to broadly support horseshoe crab conservation.

Few people understand how deeply the TAL/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. The safety of much of the world's pharmaceutical and medical devices must be tested for the presence of life-threatening endotoxins prior to public use, and the most reliable endotoxin detection test currently available is TAL/LAL. There is no indication that the world's human and animal population will become less dependent on medical services in the years to come. In fact, as our global population expands, ages, and medical advancements improve and/or prolong life, we expect to become more, not less reliant upon endotoxin detection methodologies, which currently means TAL or LAL. It is questionable whether current harvesting levels for TAL/LAL can be sustained, much less meet the projected future demands of this rapidly growing market, particularly if Asian horseshoe crab species are harvested to functional extinction.

27.2 Projected TAL/LAL Market Growth

Demand for TAL/LAL to test biomedical devices and vaccines is likely to rise significantly in the next two decades. Approximately 25 % of the medical device market is currently dependent upon TAL/LAL for endotoxin detection. Although the medical device market is about half the size of the world's pharmaceutical market (~$350 billion USD annually), it is showing rapid growth, driven in part by greater life expectancy and an aging population. Although vaccines are a small segment of the global pharmaceutical market, they represent the fastest growing segment of this industry and are heavily reliant upon endotoxin detection. According

to the World Health Organization (WHO) the vaccine market's projected growth over the next 15 years is 10–15 % annually, vs. 5–7 % for pharmaceuticals. And these figures do not include the rapidly growing veterinary vaccine market. According to WHO, in 2007 global vaccine sales were $19 billion USD; by 2010 they had grown to $28 billion USD and are projected to reach $100 billion USD by 2025.

Much of this growth will occur in emerging markets, in countries such as China, India and Brazil (IMS 2012). An emerging market is defined as the percentage of growth into the $5,000 USD or above income bracket. These individuals are assumed to have access to medical services previously unavailable to them. China's income growth, by this definition, dwarfs all other emerging markets combined (IMS 2012).

The size of the pharmaceutical market in 2006 was $658 billion USD with emerging markets representing 14 %. By 2011 it had grown to $956 billion USD with emerging markets representing 20 %. The projected growth for 2016 is $1,175–1,205 billion USD with emerging markets representing 30 % (IMS 2012). Here again these emerging markets represent many of the same Asian countries that are experiencing rapid growth in the vaccine market.

Currently, the medical device market is dominated by U.S. companies making up approximately 45 % of total revenue, with Europe coming in second at approximately 25 %. However, the Asian market is growing rapidly. Countries such as China, India and Brazil are responsible for producing more than 86 % of the world's vaccines by volume, with growth projected to 87 % by 2020 (Visiongain 2010). China, the world's largest vaccine producer, produces more than one billion vaccine doses annually and is preparing to take on a larger role in the international vaccine market. With the world's largest population and 17 million newborn babies each year (Central Intelligence Agency 2014), growing demand is not surprising. Considering the global use of vaccines alone illustrates how reliant consumers are on horseshoe crabs via the endotoxin detection industry, and in emerging markets a large percentage of endotoxin detection is dependant upon TAL, derived from the two species of horseshoe crabs (*Tachypleus tridentatus* and *T. gigas*) that are in serous decline.

There is a growing trend to outsource product manufacturing to emerging markets, which may make good economic sense, if it were not for the fact that a good portion of these emerging markets are dependent upon the blood of the two Asian horseshoe crab species that are in serious decline.

While not all pharmaceutical products are tested with TAL/LAL, any product or device that comes in contact with blood, lymph, spinal fluids or mucus membranes (i.e., products that do not pass through the body via an oral pathway) is tested for the presence of endotoxins. There is also a considerable amount of endotoxin detection utilized in the research and development of new products. For every 250 drugs that make it to preclinical testing, only one may make it to FDA approval.

Unfortunately, it is difficult to obtain reliable data on the size of the TAL/LAL industry itself, in terms of annual revenue. However, the size of the TAL/LAL market is not really important, but rather the size of the market they serve, for it is growth on the consumer side that places pressure on the horseshoe crab resource needed for endotoxin detection.

27.3 Meeting Growing Demand

Can the world's horseshoe crab population meet the growing demands of the global healthcare industry? Although we lack definitive data on the size and health of the Asia horseshoe crab population, by all accounts, it is diminishing (IUCN SSC Horseshoe Crab Specialist Group, personal communication). Yet the Asian healthcare industry is growing at an unprecedented level, and is largely dependent upon TAL derived from *Tachypleus tridentatus* or *T. gigas* for endotoxin detection.

In the United States, home to *Limulus*, the harvest of horseshoe crabs for the LAL industry is regulated by the Atlantic States Marine Fisheries Commission (ASMFC), which is tasked with implementing the Interstate Fishery Management Plan (FMP) for the horseshoe crab (ASMFC 1998). In 1998, the FMP established a biomedical mortality threshold, which could trigger action by the Management Board if exceeded (ASMFC 2013). With the United States horseshoe crab population just beginning to show signs of recovery after years of decline, it is questionable whether the US horseshoe crab population can manage the growth of the LAL consumer market, much less the TAL consumer market, if there were to be an issue of supply and demand. Is it wise to have the global healthcare industry so directly tied to a diminishing and/or marginally stable resource?

The challenges for the three Asian species are much more complex; their ranges are extensive (Fig. 27.1) and encompass a host of countries with very different social, economic and environmental priorities. We have a considerable amount of information about the species in areas where the population has declined, but much less information about the species in areas where the population appears reasonably healthy. It is these areas of relative health that are of major concern, for as the need for TAL grows, and the resources in traditional harvesting areas decline, these healthy, often unregulated populations will be the first to be exploited, if they are not being exploited already.

27.4 Fisheries Management

As the result of serious decline in the American horseshoe crab population during the 1990s, the ASMFC, a governmental regulatory body represented by each of the states along the East Coast of the United States, implemented an Interstate FMP. This plan, focused on the sustainability of the species, has been revised seven times since its inception, to keep pace with changing conditions in the horseshoe crab population. Built into this plan is a biomedical exemption based on an estimated bleed and release mortality of 57,500 horseshoe crabs, which is calculated at 15 % of the total biomedical harvest.

To meet the projected healthcare industry demand, it is likely that the allowable mortality threshold set for *Limulus polyphemus* will have to be raised or the level of estimated mortality associated with biomedical harvest reduced. LAL producers

Table 27.1 Number of horseshoe crabs harvested for LAL production and the estimated number lost due to the bleeding process (assuming 15 % mortality) each year from 2005 to 2012

	2005	2006	2007	2008	2009	2010	2011	2012
Harvested for LAL	323,149	367,914	500,251	511,478	512,552	548,751	628,476	611,827
Total mortality	44,830	49,182	63,432	63,285	60,642	75,428	80,827	79,786

Source: ASMFC

have been able to manage market growth by improving the industries harvesting, handling and release protocols, as well as through advancements in manufacturing and testing methodologies. With production waste now at a minimum and testing methodologies fine-tuned, LAL producers will likely need to harvest more animals to keep pace with global demand. Under current regulations, however, there is no further allowance for increased harvest. Every year since 2005, biomedical harvest for LAL production has increased, and every year since 2007, LAL producers have exceeded the mortality threshold set by the ASMFC (Table 27.1). A review process is underway to determine what if anything should be done to enforce the proposed mortality limit.

Two of the three Asian horseshoe crab species are used in the production of TAL, *Tachypleus tridentatus* and *Tachypleus gigas*. TAL is only produced in China and used primarily in China, some in Russia, very little in India and hardly any in Japan, South Korea and South East Asia. Chinese multi-national pharmaceutical and medical device companies that manufacture in China, yet sell worldwide, purchase and test their end products with LAL. However, with the world's largest population of over 1.3 billion people, one fifth of the earth's population, and the largest aging population in the world, China by itself, is a sizable healthcare market.

Unfortunately, we do not have reliable horseshoe crab harvesting figures for China's TAL industry, nor knowledge of how it may be regulated. We are only just beginning to gather data on where, outside of China, *Tachypleus* is harvested for TAL.

Tachypleus is generally harvested in pairs, and bled to death, then sold to a secondary market for human consumption and chitin, resulting in 100 % mortality. The limited available harvesting numbers suggest a drop in abundance from 600,000 pairs 5–10 years ago, to less than 100,000 pairs currently. With the three Asian horseshoe crab species trending towards decline, how will TAL producers keep pace with their countries growing health care market?

The demand for horseshoe crabs throughout its Asian spawning range is placing significant stress on the species and hindering conservation efforts. Although we do not yet have sound data on the health of the three Asian horseshoe crab species, we do know that the horseshoe crab populations in Japan, Taiwan, China, Hong Kong and Singapore, once vibrant, are now endangered.

27.5 Conclusion

Without a regulatory process on TAL similar to what is in place for LAL, the current rate of harvest for *Tachypleus* is unsustainable. Failure to address this problem will continue to add to the decline of Asian horseshoe crab species, and shift the harvest pressure onto the US LAL market to absorb the residual demand. As a result of sound US management policies implemented since 1999, *Limulus* is beginning to recover. It is questionable, however, whether the LAL industry can offset a decline in TAL availability in a rapidly growing healthcare market, even if regulations are loosened to allow greater harvest and, in turn, greater mortality of *Limulus polyphemus* stocks.

Investment in the development and utilization of alternative endotoxin detection methodologies that reduce or avoid reliance on live horseshoe crabs is the ideal solution to ensure the sustainability of the endotoxin detection industry, their consumer supply line, and horseshoe crab populations world-wide. The question is whether the pharmaceutical and medical device industry will drive this transition. By choosing vendors who use best practices for TAL and LAL production, supporting global supply chain initiatives that integrate social and environmental considerations into the qualification and choice of vendors, as well as offering or developing alternative testing methods, industry leaders have the potential to drive the TAL/LAL industry toward the reduction of animal-based testing and make a significant contribution to global conservation of the horseshoe crab species. Recommended best practices include moist and temperature-controlled transport, prescreening for injured crabs, separating crabs to avoid re-bleeding, aseptic environments and sterile needle use, and returning bled crabs to their point of origin. In 2014, ERDG launched a new section on their website called “Protecting Health.” The web content is designed to delineate the problems outlined in this paper, raise awareness of the possible implications for global health industry, and provide tools to promote communication regarding how the biomedical industry can become a driving force behind the conservation of the world’s four horseshoe crab species.

References

ASMFC (Atlantic States Marine Fisheries Commission) (1998) Interstate fishery management plan for horseshoe crab. Atlantic States Marine Fisheries Commission, Fishery Management Report No 32. Washington, DC

ASMFC (Atlantic States Marine Fisheries Commission) (2013) Horseshoe crab stock assessment update 2.2

Botton ML, Ropes JW (1988) An indirect method for estimating longevity of the horseshoe crab (*Limulus polyphemus*) based on epifaunal slipper shells (*Crepidula fornicata*). J Shellfish Res 7:407–412

Botton ML, Loveland RE, Tiwari A (2003) Distribution, abundance, and survivorship of young-of-the-year in a commercially exploited population of horseshoe crabs *Limulus polyphemus*. Mar Ecol Prog Ser 265:175–184

Carmichael RH, Rutecki D, Valiela I (2003) Abundance and population structure of the Atlantic horseshoe crab *Limulus polyphemus* in Pleasant Bay, Cape Cod. Mar Ecol Prog Ser 246:225–239
Central Intelligence Agency (2014) China. In The World Factbook. https://www.cia.gov/library/publications/the-world-factbook/geos/br.html. Accessed Sept 2013
IMS (2012) Institute for Healthcare Informatics, IMS Market Prognosis, May 2012, Economic Intelligence Unit, Jan 2012
Leschen AS, Grady SP, Valiela I (2006) Fecundity and spawning of the Atlantic horseshoe crab, *Limulus polyphemus*, in Pleasant Bay, Cape Cod, Massachusetts, USA. Mar Ecol 27:54–65
Ropes JW (1961) Longevity of the horseshoe crab, *Limulus polyphemus* (L.). Trans Am Fish Soc 90:79–80
Rudloe A (1983) The effect of heavy bleeding on mortality of the horseshoe crab, *Limulus polyphemus*, in the natural environment. J Invertebr Pathol 42:167–176
Shuster CN Jr, Botton ML (1985) A contribution to the population biology of horseshoe crabs, *Limulus polyphemus* (L) in Delaware Bay. Estuaries 8:363–372
Visiongain (2010) Vaccines manufacturing technology and services: commercial prospects 2010–2025. The Global Vaccine Market, London, 2009–2025
Walls EA, Berkson J (2003) Effects of blood extraction on horseshoe crabs (*Limulus polyphemus*). Fish Bull 101:457–459