Antibiotics in Hide Preservation and Bacterial Control *

by

George Stockman**, Dean T. Didato, Buckman Laboratories, Inc.
Elton Hurlow, Buckman Laboratories International, Inc.

1256 N. McLean Blvd.
Memphis, TN 38108

Abstract

The use of antibiotics requires careful deliberation regarding both the criteria for their selection and the methodology of their application. Certain widely available antibiotics, including Doxycycline HCl, have demonstrated activity for short-term preservation of fresh hides. By eliminating the requirement of dry salt or brine curing, there are potential major benefits from reduced environmental burden. When used in the soak, such antibiotics may prove to be an economical alternative to conventional antimicrobials currently used for this purpose.

However, evaluation of the use of clinically significant antibiotics must take into consideration other factors besides efficacy in hide preservation or bacterial protection during soaking. In particular, we must consider potential long-term risks associated with non-therapeutic applications of molecules that have been shown to be effective human antibiotics.

Before adopting widespread use of clinical antibiotics in hide preservation and soaking, it would be sensible to weigh the benefits and the potential consequences of such uses in the broadest context of global health, politics, and business decision-making. This paper will explore the use of antibiotics in industry and will discuss widely differing viewpoints on the subject. The widespread use of antibiotics for promotion of the general health and growth of food-producing animals will be reviewed. Such uses account for approximately 70% of the antibiotics and other antimicrobials used in the United States and are the subject of vigorous ongoing debate. Antibiotic usage for hide preservation and soaking protection will likely undergo similar scrutiny.

Clear guidance has been provided by the World Health Organization Alliance for the Prudent Use of Antibiotics. Adoption of these policies by nations around the world is occurring at a slow yet measured pace. Industrial uses of antibiotics offer obvious immediate environmental benefits, offset by possible long-term compromised viability against significant human diseases. This disparity presents members of the hide and leather industries with an interesting opportunity to test Environment, Safety and Health Policies, as well as Corporate Vision.

Abstracto

El uso de antibióticos requiere una deliberación cuidadosa con respecto a los criterios para su selección y a la metodología de su uso. Ciertos antibióticos disponibles y empleados en extenso, incluyendo Doxiciclina HCl, han demostrado actividad para la preservación a corto plazo de pieles frescas. Eliminando el requerimiento de sal seca o de la salmuera para la conservación, hay ventajas potenciales importantes para la reducción de la carga ambiental. Cuando son empleados en el remojo, tales antibióticos pueden demostrar ser una alternativa económica a los antimicrobianos convencionales usados actualmente para este propósito.

Sin embargo, la evaluación del uso de antibióticos clínicamente significativos debe tomar en consideración otros factores además de la eficacia en la preservación de la piel o de la protección bacteriana durante el remojo. En particular, debemos considerar riesgos potenciales a largo plazo asociados a usos no terapéuticos de moléculas que han demostrado ser eficaces antibióticos para los seres humanos.

* A Technical Note based on a presentation at the 102nd annual meeting of the American Leather Chemists Association at the Hyatt Regency, Milwaukee, WI on June 23, 2006

** Corresponding Author - E-mail: gbstockman@buckman.com

Manuscript received July 5, 2006 and accepted for publication on August 8, 2006

Antes de adoptar el uso extendido de antibióticos clínicos en la preservación de la piel y remojo, sería sensible pesar las ventajas y las consecuencias potenciales de tales aplicaciones en el contexto más amplio de la salud, de la política, y de la toma de decisiones globales del negocio. Este estudio explorará el uso de antibióticos en industria y discutirá ampliamente los diferentes puntos de vista sobre este tema. El uso extendido de los antibióticos para la promoción general de la salud y del crecimiento de animales que se producen para alimentación será revisado. Tales aplicaciones aplican en el 70% aproximadamente de los antibióticos y de otros antimicrobianos usados en los Estados Unidos y son el tema de vigorosa discusión en curso. El uso de antibióticos para la preservación de la piel y la protección del remojo experimentará probablemente un escrutinio similar.

La Alianza de la Organización Mundial de la Salud ha proporcionado claras direcciones para el uso prudente de antibióticos. La adopción de estas políticas por las naciones alrededor del mundo está ocurriendo aún a paso lento. Las aplicaciones industriales de antibióticos ofrecen obvias ventajas ambientales inmediatas, compensadas por un posible compromiso de viabilidad a largo plazo contra enfermedades humanas significativas. Esta disparidad presenta a miembros de las industrias de la piel y del cuero con una interesante oportunidad de probar políticas sanitarias de medio ambiente, seguridad, así como la de visión corporativa.

INTRODUCTION

Short term preservation of hides and skins remains an important need for our industries. Around the World, the most common method of preservation - salt curing - is under pressure. It's most significant shortcoming is the limitation of disposal options, due to the build up of total dissolved solids in surface waters. These dissolved solids limit the usefulness of impacted water resources for domestic consumption and agriculture.

For the packer and hide processor, there are reasonable alternatives to salt curing, including: chilling, refrigeration, air drying and a wide range of commercial bactericides. New technologies are also under development that will minimize the activity of the proteolytic enzymes originating from bacterial and autolytic processes. Amidst these options is the potential for the use of a class of antimicrobial chemotherapeutic agents, commonly referred to as antibiotics, for short term preservation of hides and skins.

There are two categories of antimicrobial chemotherapeutic agents[1] used to control bacteria: antibiotics and synthetic drugs. I take the liberty of combining the two categories by referring to them collectively in layman's terminology, as "antibiotics".

Figure 1

Antibiotics are drugs that function by selective toxicity, assuring that the substance inhibits or kills the intended pathogen, without seriously harming the host.

Buckman Laboratories in Brazil has done extensive laboratory testing of a wide range of potential options for short term hide preservation. Such an approach should effectively eliminate the use of common salt for preservation. The substances tested include conventional antibacterials, such as dithiocarbamates, as well as non-conventional substances like antibiotics and enzyme inhibitors.

EXPERIMENTAL AND RESULTS

Associates at our Leather Center of Excellence in Franca, Brazil tested a wide range of antibiotics to identify their effectiveness in short term hide preservation. In this initial screening, 14 antibiotic preparations were tested at equal cost levels, along with five other chemical preservatives and a control. Raw hide pieces were dipped in solutions of the various hide preservative treatments, were allowed to drain, and were incubated at 30 deg. C. The hide pieces were evaluated for hair slip and odor after 4, 24, 48 and 72 hours, as shown in Figure 1. Samples from the hide pieces were plated on PCA medium with 8.5% sodium chloride for Halotolerant microorganisms at the same intervals. These were incubated for 48-hours at 37 degrees C.

As seen in Table 1, most of the treatments protected the hides from hair slip and odor development for 24-hours, but none offered 48-hours protection under the conditions of the test. The bacterial counts for several of the treatments were surprisingly high, even after only 4-hours of storage, as shown in Figure 2. The control showed significant bacterial activity after 4-hours, as shown in Figure 3. After 24-hours storage, more than half of the treatments showed significant bacterial growth, as seen in Figure 4. Finally, after 72-hours only six of the treatments resulted in very little or no bacterial growth, as shown in Figure 5. Interestingly, while these plates were negative or minimal for bacteria, in every case significant hair slip and odor were observed.

The best performers of the antibiotics were included in a second laboratory evaluation that compared hundreds of substances and combinations of non-antibiotic substances

TABLE 1

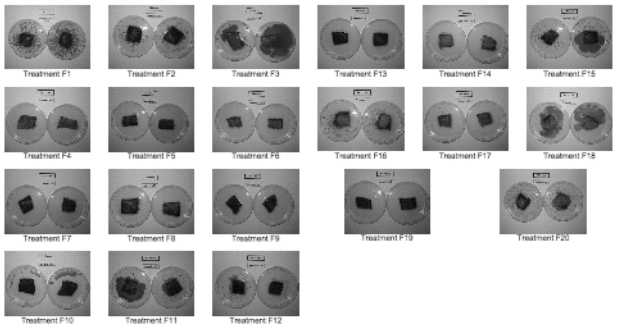
Short Term Preservation of Hides and Skins
Buckman Laboratorios LTDA.
Campinas, SP, Brasil

Evaluation of Common Antibiotics

Treatment	Description	Results - Equal Cost Basis (hours)
F1	Control	<24
F2	Busan 1251	24
F3	BSP 2454 + BSN 1125 (PE-2063)	24
F4	Commercial Antibiotic Product	</= 24
F5	Commercial Antibiotic Product	24
F6	Bactericide	24
F7	Antibiotic	24
F8	Antibiotic	24
F9	Antibiotic	24
F10	Antibiotic	24
F11	PE-1962	24
F12	Antibiotic	24
F13	Antibiotic	24
F14	Antibiotic	24
F15	Antibiotic	24
F16	Antibiotic	24
F17	Antibiotic	< 24
F18	Antibiotic	24
F19	Busan 1426	24
F20	Antibiotic	24

Note: All treatments yielded significand odor and hair slip by 48 hours

Figure 2



Bacterial Growth After 4-hours

following the same procedure previously described.

As seen in the Table 2, widely used commercial bactericides, when they are used on their own, provide up to 30-hours of protection. This should be acceptable for situations where hides are to be soaked the day after slaughter and flaying. These commercial bactericides have found increasing use, especially in conjunction with chilling and in-transport refrigeration, for short term protection.

Buckman-Brazil has observed that combinations of certain widely used clinical antibiotics provide excellent efficacy in the role of short term hide preservation. Others have recognized this fact and as a result, doxycycline has found its way into the hide preservation market in South America. In spite of their extremely high price per pound, the low dosage requirements provide 48-hour preservation at a competitive application cost.

For some of the conventional alternatives explored, inherent disadvantages, such as formaldehyde toxicity and collagen reactivity, preclude their practical application.

Alternative Technology

Fortunately, there are alternatives to either conventional commercial bactericides or to antibiotics. A new approach to short term preservation has been pioneered by Buckman. This Buckman technology incorporates inhibitors that can deactivate proteolytic enzymes released during skin autolysis as well as the extra cellular proteases released by bacteria. Thus collagen destruction is minimized, even when the bacterial population is allowed to grow. When used in combination with conventional commercial bactericides, these enzyme inhibitors provide a synergistic effect on hide preservation. On the one hand, bacterial growth is regulated by antimicrobials, while on the other, enzymatic attack of the collagen is mitigated. Such an approach may protect hides for 48-60 hours, depending on temperature.

IMPLICATIONS AND DISCUSSION

There are numerous approaches to short term preservation, all with technical merit. Due to the economics involved, antibiotics are a tempting alternative. In light of these results, why then has there only been limited application of antibiotics for hide preservation. The answer lies in a difficult combination of political, legal and ethical considerations.

Recent news reports have warned that a dangerous new strain of methicillin-resistant Staphylococcus aureus (MRSA)[2,3] that previously was only found in hospitals has now impacted communities at large. According to the U.S. Centers for Disease Control and Prevention (CDC), this newly resistant and highly virulent strain of Staphylococcus accounts for 126,000 hospitalizations per year in the USA alone; up to a quarter of these individuals may in fact die.

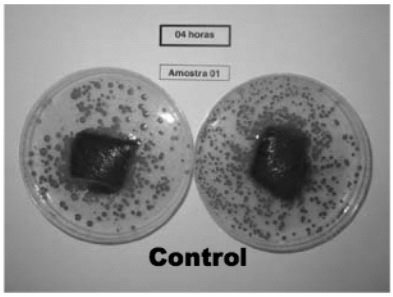
The popular drug Keflex® has long been a doctors' favorite for combating such Staphylococcus infections. With development of resistance, so called community-associated methicillin-resistant Staphylococcus aureus is controlled in hospitals with vancomycin as a last line of defense.

At Texas Children's Hospital in Houston, where 1,700 children are admitted with Staphylococcus infections annually, the hospital assumes that the infection is resistant. Such drug-resistant bacteria are difficult and much more costly to treat than non resistant organisms.

Numerous other clinically significant antibiotics are at risk due to the development of resistance. One of the most notable is Cipro®, which is the drug of choice to combat respiratory Anthrax infections. This concern was front page news when the U.S. Armed Services was concerned about the prospects of facing Anthrax as a biological warfare agent in Iraq.

We must note that while there is clear evidence of a dangerous global trend in the resistance to some therapeutically important antibiotics, it is highly unlikely that resistance will be an issue for conventional commercial bactericides used in hide preservation. King *et al.*[4] reported that industrial microbicides differ from antibiotics mainly in the former's devastating mode of action.

Figure 3



Bacterial Growth After 4-hours

Global View

The World Health Organization (WHO) sounded the alarm over the resistance of disease causing organisms to antibiotics in a 2001 report of its Alliance for the Prudent Use of Antibiotics[5]. The group reported that: "…bacteria have emerged that are resistant to each of the antibiotics currently on the market." WHO notes that: "Antibiotics are used, not only to combat bacterial infections in animals, but also as growth promoters in animals raised for meat" They claim that, "A reservoir of antibiotic resistance is building in the bacteria associated with animals which may be transferred to bacteria living in humans." Many of the WHO recommendations deal with increasing awareness and improved surveillance. The recommendation most important for tanners though, is that antibiotic use in animals should be regulated.

The WHO's findings are having a profound effect on the progress of antibiotic usage worldwide.

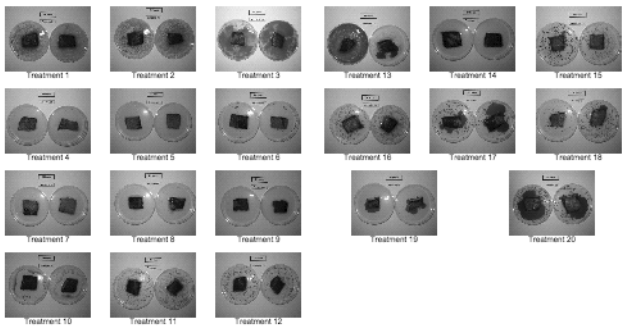
U.S. Position

In the United States, there is increasing substantiation of antibiotic resistance as a significant public health threat[6]. In 1998, the National Academy of Sciences[7] noted that infections caused by antibiotic-resistant bacteria result in minimum costs of $4-5 billion annually to US citizens. An estimated 70% of antibiotics used in the United States, and perhaps 50% worldwide, are fed to farm animals for nontherapeutic purposes, typically including stress management and growth promotion. In the United States, there is no requirement for a prescription for such use.

Antibiotics are becoming ubiquitous. The United States Geological Survey Toxic Substances Hydrology Program[8] has reported that antibiotics were found in 48% of the 139 streams it tested nationwide. They noted that half of these occurrences were downstream from agricultural operations, including poultry, swine, dairy and cattle operations.

In the United States, The Interagency Task Force on Antimicrobial Resistance is on a parallel track to that of WHO. The task force is co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH). The Task

Figure 4



Bacterial Growth After 24-hours

Force's report[9], released in January 2001, provides a blueprint for federal actions to address the emerging threat of antibiotic resistance. It identifies four major needs: Surveillance, Prevention and Control, Research, and Product Development.

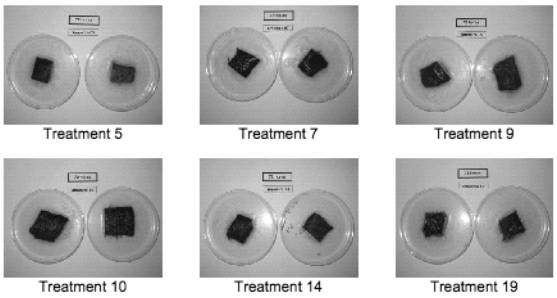
One of the Prevention and Control measures proposed by the Interagency Task Force is an FDA Regulatory Framework for Antimicrobial Drugs in Food Animal Production. FDA's resulting pre-approval assessment strategy provides an approach for evaluation of drugs according to their importance in human medicine. It also applies to drug use in food-producing animals. According to FDA[10], they have "the option of not approving a drug if the risk of a public health consequence is too high."

A risk assessment conducted by FDA's Center for Veterinary Medicine (CVM), covering the use of fluoroquinolones in poultry has recently been completed. A major example of a fluoroquinolone is enrofloxacin marketed in the US as Baytril®. Baytril is the animal counterpart of the better known antibiotic, ciprofloxacin, which is marketed under the brand name Cipro®. As a result of their risk assessment, the Center for Veterinary Medicine proposed withdrawing approval of fluoroquinolones for use in poultry[11]. On July 29, 2005 the Commissioner of the FDA issued a final decision banning the use of enrofloxacin in poultry in the United States.

The FDA Commissioner found that the proportion of Campylobacter infections that are resistant to fluoroquinolones has increased significantly with the use of enrofloxacin in poultry in the US. FDA's finding is consistent with the observations in a number of other countries. Fluoroquinolone, specifically as ciprofloxacin, or Cipro, increasingly fails to successfully treat human campylobacteriosis. This failure often prolongs the duration of the disease and may increase the risk of complications.

Stix[12] reported in Scientific American that fluoroquinolones are predicted to become the largest-selling class of antibiotics by the year 2011. He notes that some strains of Shigella dysenteria, the organism that causes epidemic dysentery, have become resistant to all antibiotics but ciprofloxacin. He further

Figure 5



Bacterial Growth After 72-hours

Short Term Preservation of Hides and Skins
Buckman Laboratorios LTDA.
Campinas, SP, Brasil

Treatment	Description	Results - Equal Cost Basis (hours)
A	Control	<24
B	Microbicide + Proprietary Inhibitor*	60
C	Enzyme Inhibitor Blend	48
D	Microbicide + Proprietary Inhibitor*	48
E	Aldehyde + Bactericide	72
F	Antibiotic Combination	48
G	Formaldehyde Releaser	72
H	Proprietary Inhibitor* + Bactericide	48
I	Aldehyde	48
J	Quat Sanitizer	36
K	Polyquat Sanitizer	48
L	Bactericide	30

* Patent pending

explains that dysentery is capable of causing tens of thousands of deaths, especially in developing countries.

U.S. Regulatory Direction

While Congress took prior steps to curb antibiotic overuse in human medicine through amendments to the Public Health Service Act (42 U.S.C. 201 et Seq.), it has not addressed antibiotic overuse in agriculture. Senate Bill S. 742[13] seeks to do just that. Clearly, the specter of terrorist attacks involving infectious biological agents has entered into the collective thinking of the drafters of the bill. They find that, "…antibiotic resistance, resulting in a reduced number of effective antibiotics, may significantly impair the ability of the United States to respond to terrorist attacks involving bacterial infections or a large influx of hospitalized patients…." Thus, the purpose of the Act is "…to preserve the effectiveness of medically important antibiotics used in the treatment of human and animal diseases by phasing out use of certain antibiotics for nontherapeutic purposes in food-producing animals."

The bill is currently in the Committee on Health, Education, Labor and Pensions where it has languished since April 7, 2005. Even if the bill is not voted out of committee during the current congressional session, it represents a direction towards further regulation of antibiotics to reverse the trend in the incidence of resistance.

As might be expected, various trade and public health organizations are lining up with policy statements either in support of or in opposition to the direction of legal developments in the United States. The American Public Health Association [14] adopted APHA Resolution 9908 in 1999. This resolution noted a rapid increase in antibiotic resistance in the United States and worldwide. They also claimed that the complex nature of the problem included selective pressure of overuse and misuse of antibiotics in human medicine, and the use of subtherapeutic levels of antibiotics in animal feeds. APHA urged the FDA to adopt regulations that eliminate the non-medical use of antibiotics and limit the use of antibiotics in animal feeds. APHA has since adopted a policy that "encourages hospitals and health-care facilities, and other bulk purchasers of foodstuffs, to adopt procurement policies that encourage and, where feasible, require procurement of meat, fish and dairy products produced without nontherapeutic use of medically important antibiotics."

The American Veterinary Medical Association[16] opposes the APHA resolution, claiming that APHA's resolution does not address the importance of sanitary preparation of food as a means of preventing food borne infections. They also are concerned that there is no system to verify whether nontherapeutic antimicrobials have been used in food production and that the resolution does not consider a balanced view of the scientific literature, and fails to acknowledge the remedies provided by the FDA's Guidance for Industry.

The National Cattlemen's Beef Association[17] (NCBA) has adopted a policy on antibiotics that is very conciliatory to regulators. They promote the limitation of antimicrobial use through sound husbandry and preventative practices and call for ongoing continuing education for both producers and veterinarians in the area of judicious antimicrobial use. The cattlemen resolve to encourage producers, "to voluntarily comply with judicious antibiotic use guidelines and to encourage others to do the same."

SUMMARY

The direction in the United States is clear. Regulatory agencies and the U.S. Congress are proceeding with laws and regulations that will limit the use of antimicrobials in food-animal production. In the mean time, FIFRA effectively blocks the use of therapeutic antibiotics for hide preservation through its rigorous registration requirements.

We also must consider that regulatory developments outside the United States will take different paths. The European Union[13], for example in 1999, banned feeding of medically important antibiotics to animals other than for disease treatment or control. Sweden and Denmark[19] have completely banned the use of specific antibiotics in animal feed as growth promoters, reportedly with no significant impact on animal health or productivity, food safety, or meat prices. In these countries, levels of resistant bacteria have been reported to have declined.

Companies will make decisions whether to use antibiotics for short term hide preservation based largely on their evaluation of the technical merits of the products offered. Such a decision must be consistent with the vision that management has for your company. At Buckman Laboratories our Code of Ethics is an integral part of our Vision and Mission. Buckman's Code of Ethics makes it clear "that we must use the highest ethics to guide our business dealings and to ensure that we are always proud to be a part of Buckman Laboratories." It also directs "that we will discharge the responsibilities of corporate and individual citizenship to earn and maintain the respect of the community." Finally, our *Environmental Philosophy Statement* requires that we "Conduct all of our business operations in such a way as to minimize any risk of adverse impact on the community and the environment."

As long as specific antibiotics provide demonstrated benefit to humans against pathogens, we cannot promote their use for hide preservation or bacterial control during soaking. Not withstanding Buckman's position, each stakeholder in the hide and skin supply chain must come to grips with this relevant issue. That decision should weigh the benefits and potential consequences of such uses in the broadest context of global health, politics and ethical decision-making.

ACKNOWLEDGEMENTS

The authors wish to thank Paulo Sergio Beltrao, Rossana Chiocca and Renato Bettanin of Buckman's Leathermaking Technologies team in Brazil for their technical contribution and guidance in the preparation of this paper.

REFERENCES

1. Keyser, Gary E.; The Community College of Baltimore County, Biology 230 Lecture, Unit IV: Microbial Genetics and Microbial Metabolism.
2. USA Today; Superbugs spread fear far and wide. May 11, 2006.
3. Dow Jones Newswires, January 28, 2006.
4. King, Vanja M., Bryant, Stephen D., and Haque, Mainul N.; Fact and fantasy regarding resistance to microbicides. *JALCA*, **96**, 162-168, 2001.
5. World Health Organization - Alliance for the Prudent Use of Antibiotics; Antibiotic resistance: synthesis of recommendations by expert policy groups.
6. Senate Bill 742, 109 Congress of the United States of America; Introduced April 7, 2005.
7. Institute of Medicine of the National Academies (formerly National Academy of Sciences); Antimicrobial drug resistance: issues and options (Workshop Report); Washington: National Academy Press, 1998.
8. USGS Fact Sheet FS-027-02 (June 2002); Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams.
9. Interagency Task Force on Antimicrobial Resistance; A public health action plan to combat antimicrobial resistance, Part 1: domestic issues; January 2001.
10. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine; Guidance for industry # 152: Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. October 23, 2003.
11. U.S. Food and Drug Administration, Department of Health and Human Services; Final decision of the commissioner - Docket No. 2000N1571: Withdrawal of approval of the new animal drug application for enrofloxacin in poultry. July 29, 2005.
12. Stix, Gary; An Antibiotic Resistance Fighter. *Scientific American*, Vol. 294, No.4 (80-83), April 2006.
13. Senate Bill 742; *op. cit.*
14. APHA Resolution 9908; Addressing the problem of bacterial resistance to antimicrobial agents and the need for surveillance. Adopted November 10, 1999.
15. APHA Policy 2004-13; Helping preserve antibiotic effectiveness by stimulating demand for meats produced without excessive antibiotics. November 9, 2004.
16. American Veterinary Medical Association; Board opposes APHA resolution against nontherapeutic antimicrobial use in food animals. *Journal of the American veterinarian Association* - News, June 1, 2004.
17. National Cattlemen's Beef Association; NCBA antibiotic policy: Judicious Use of Antibiotics. 2003 Cattle Health Archive, CH 3.12.
18. Senate Bill 742; *op. cit.*
19. World Health Organization, *op. cit.*