# *Disinfection, Sterilization, and Preservation*

Fourth Edition

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SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000002

# Contents


Part I Introduction

1. Historical Review 3
   *Seymour S. Block*
2. Definition of Terms 18
   *Seymour S. Block*

Part II Fundamental Principles of Activity

3. Principles of Antimicrobial Activity 27
   *A. D. Russell*
4. Physical Factors Influencing the Activity of Antimicrobial Agents 59
   *Harry B. Kostenbauder*
5. Kinetics of the Inactivation of Microorganisms 72
   *G. B. Wickramanayake and Otis J. Sproul*
6. Principles of the Thermal Destruction of Microorganisms 85
   *I. J. Pflug and R. G. Holcomb*

Part III Disinfectants and Antiseptics. A. By Chemical Type

7. Chlorine and Chlorine Compounds 131
   *G. R. Dychdala*
8. Iodine and Iodine Compounds 152
   *W. Gottardi*
9. Peroxygen Compounds 167
   *Seymour S. Block*
10. Disinfection and Sterilization by Ozone 182
    *G. B. Wickramanayake*
11. Alcohols 191
    *Elaine L. Larson and H. E. Morton*
12. Phenolic Compounds 204
    *D. O. O'Connor and J. R. Rubino*
13. Quaternary Ammonium Antimicrobial Compounds 225
    *John J. Merianos*
14. Surface-Active Agents: Acid-Anionic Compounds 256
    *G. R. Dychdala and John A. Lopes*
15. Surface-Active Agents: Amphoteric Compounds 263
    *Seymour S. Block*
16. Chlorhexidine 274
    *G. W. Denton*
17. Nitrogen Compounds 290
    *H. W. Rossmoore*




SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000003

18. Polymeric Antimicrobial Agents 322
*Oscar W. May*
19. Mercury—Industrial Uses as Preservatives 334
*Robert A. Opperman*
20. Organotin Compounds 344
*M. H. Gitlitz and C. B. Beiter*
21. Copper and Zinc Preservatives 358
*Charles C. Yeager*

Disinfectants and Antiseptics. B. By Type of Microorganisms

22. Chemical Sporicidal and Sporostatic Agents 365
*A. D. Russell*
23. Mycobacterial Disinfection and Control 377
*Jeffrey Rubin*
24. Fungistatic and Fungicidal Compounds for Human Pathogens 385
*Ernest M. Walker, Jr. and Glenn R. Gale*
25. Principles of Viral Control and Transmission 411
*Herbert N. Prince, Daniel L. Prince, and Richard N. Prince*
26. Measures for Disinfection and Control of Viral Hepatitis 445
*O. Thraenhart*
27. Human Immunodeficiency Virus (HIV) Disinfection and Control 472
*Jeffrey Rubin*
28. Antiprotozoan, Antihelmintic, and Other Pest Management Compounds 482
*S. E. Leland, Jr.*

Part IV Chemical and Physical Sterilization

29. Sterilization by Heat 495
*L. J. Joslyn*
30. Sterilization Filtration 527
*R. V. Levy and T. J. Leahy*
31. Sterilization by Ultraviolet Irradiation 553
*I. L. Shechmeister*
32. Sterilization and Preservation by Ionizing Irradiation 566
*G. J. Silverman*
33. Sterilization with Ethylene Oxide and Other Gases 580
*Anthony N. Parisi and William E. Young*
34. Glutaraldehyde 596
*E. M. Scott and S. P. Gorman*

Part V Medical and Health-Related Applications

35. Chemical Disinfection of Medical and Surgical Materials 617
*M. S. Favero and W. W. Bond*
36. Surgical Antisepsis 642
*D. H. M. Gröeschel and Timothy L. Pruett*
37. Infection Control: Applying Theory to Clinical Practice 655
*Inge Gurevich*

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000004

38. The Epidemiology and Prevention of Nosocomial Infections 663
*Consuelo M. Beck-Sague and William R. Jarvis*
39. Sterilization, Disinfection, and Asepsis in Dentistry 676
*Chris H. Miller and Charles John Palenik*
40. Germ-free Technology 696
*Nobuhiko Ohnishi and Shogo Sasaki*
41. Disinfection of Drinking Water, Swimming Pool Water, and Treated Sewage Effluents 713
*Christon J. Hurst*
42. Infectious Medical Wastes: Treatment and Sanitary Disposal 730
*Seymour S. Block*
43. The Hazard of Infectious Agents in Microbiologic Laboratories 749
*R. W. McKinney, W. E. Barkley, and A. G. Wedum*

Part VI Antimicrobials in Food Sanitation and Preservation

44. Antimicrobial Agents Used in Agriculture 759
*R. J. Lukens*
45. Food- and Water-Infective Microorganisms 773
*John A. Lopes*
46. Sanitation in Food Manufacturing Operations. 791
*H. W. Walker and W. S. LaGrange*
47. Chemical Food Preservatives 802
*Peggy M. Foegeding and Francis F. Busta*
48. Aseptic Packaging 833
*B. von Bockelmann*
49. Disinfection and Disease Prevention in Veterinary Medicine 846
*P. J. Quinn*

Part VII Antimicrobial Preservatives and Protectants

50. Preservation of Medicines Against Microbial Contamination 871
*Reza A. Fassihi*
51. Preservation of Cosmetics 887
*F. Sharpell and M. Manowitz*
52. Preservatives for Industrial and Miscellaneous Products 901
*Seymour S. Block*
53. Preservation of Metals from Microbial Biocorrosion 948
*Jose Rafael Sifontes and Seymour S. Block*

Part VIII Miscellaneous Topics

54. Federal Regulations of Antimicrobial Pesticides in the United States 977
*Arturo E. Castillo*
55. Facilities for Control of Microbial Agents 987
*G. Briggs Phillips and Robert S. Morrissey*
56. Marketing Overview of Specialty Biocides 999
*Anthony J. Marisca*

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000005

## Part IX Methods of Testing

57. Methods of Testing Disinfectants 1009
*A. Cremieux and J. Fleurette*

58. Methods of Testing Antiseptics: Antimicrobials Used Topically in Humans and Procedures for Hand Scrubs 1028
*M. K. Bruch*

59. Sterility Testing—Validation of Sterilization Processes and Sporicide Testing 1047
*Gordon S. Oxborrow and Robert Berube*

60. Methods of Testing Sanitizers and Bacteriostatic Substances 1058
*Robert Berube and Gordon S. Oxborrow*

61. Methods of Testing Fungicides 1069
*C. George Hollis*

62. Methods of Testing Virucides 1076
*John H. S. Chen*

63. Methods of Testing Protozoacides and Antihelmintics 1094
*S. E. Leland, Jr.*

64. Effective Use of Liquid Chemical Germicides on Medical Devices: Instrument Design Problems 1097
*W. W. Bond, B. J. Ott, K. A. Franke, and J. E. McCracken*

65. Microorganisms, Sick Buildings, and Building Related Illnesses 1107
*Seymour S. Block*

Index 1121

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000006

## CHAPTER 2

# DEFINITION OF TERMS

S.S. Block

Words are meant to convey meaning, but we cannot be sure that any word will convey the same meaning to every person. People have different backgrounds and outlooks and derive different meanings from the same word. Further, language is, in a sense, a living organism, and words change their meaning with time. Thus we have some trouble reading Shakespeare and even more with Chaucer. It is said that if something looks like a duck, quacks like a duck, and waddles like a duck, it is a duck. This is not necessarily so. Most people think they know what the term "whiskey" means, but they could be wrong, for it is a word with a legal as well as a popular meaning. Legally, whiskey is a malted beverage made from small grains distilled in a certain way, containing a certain amount of ethyl alcohol, and aged in new, charred-oak barrels. A product having the same color, odor, taste, and chemical composition might not satisfy the legal definition.

Definitions are man-made; they do not come to us from on high. They attempt to make boundaries around terms but these boundaries are often vague and indistinct. Yet we must work with them as best we can. Death is not exact. When is a person dead? When he is no longer breathing? When he is brain dead? When all the cells in his body are dead? When is a product sterile? When all life in it has been killed or when it has been heated at x temperature for y minutes or when its microbial population is reduced by z D values? It is what we say it is according to the way we construct our definition.

Definitions by lexicographers and lawyers serve the useful purpose of giving all persons the opportunity of common understanding of what they mean when they use a word. When manufacturers label a product as an antiseptic or disinfectant, it is imperative that their product does what these terms say it should do. Under the original Food and Drugs Act, a judicial decision states, "Language used in the label is to be given the meaning ordinarily conveyed by it to those to whom it was addressed." This is difficult to do where meanings are vague. Dictionaries and legal definitions clarify the meanings and give them greater stability. Words such as "antiseptic," "disinfectant," and "sanitizer" are excellent examples of words that had loosely accepted meanings until they were more strictly defined. Austin M. Patterson, a lexicographer of scientific terms, made a thorough study of many of these words in 1932, which served to crystallize their meanings. Many of the definitions that follow are of his preparation. Some of the others are from Reddish (1957) and various dictionaries, with comments by myself.

### *Disinfectant*

**A disinfectant is an agent that frees from infection,** usually a chemical agent but sometimes may be a physical one, such as x rays or ultraviolet light, that destroys disease or other harmful microorganisms but may not kill bacterial spores. It refers to substances applied to inanimate objects.

The legal definition (Reddish, 1957) is similar but more detailed: An agent that frees from infection; usually a chemical agent that destroys disease germs or other harmful microorganisms or inactivates viruses. The term is most commonly used to designate chemicals that kill the growing forms, but not necessarily the resistant spore forms of bacteria, except when the intended use is specifically against an organism forming spores or a virus, in which case the spores, too, must be killed or the virus inactivated. Proper use of a disinfectant is contingent upon the purpose for which it is employed or the type of infectious agent that there is reason to suspect may be present.

***Comments.*** The word "disinfect" first appeared in the seventeenth century when certain "effluvia" or mysterious emanations were thought to cause disease and could be destroyed by chemical substances such as burning sulfur. Because disease was associated with foul odors, disinfectants were expected to destroy or mask the odors to get rid of the infection. Patterson (1932) studied 143 definitions of *disinfectant* used from 1854 to 1930. Of

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000007

these, 25, mostly of earlier date, made no mention of microorganisms. Of the rest, 95 defined disinfectants as germ destroyers. The word still carries with it much of its original connotation, namely, the cleaning of sickrooms, clothing, bedding, lavatories, stables, etc. The use of "disinfectant" for antimicrobial chemicals used on the body, as in the case of "skin disinfectant," is frowned upon. The OTC Antimicrobial I Drug Review Panel (1974) states that disinfection properly refers to the use of such chemicals on inanimate objects and not on the human body. A hard distinction insofar as governmental regulation is concerned is that disinfectants or antimicrobial chemicals labeled for use on inanimate objects are considered economic poisons under the Federal Environmental Pesticide Control Act (7 U.S.C. 136), whereas agents such as antiseptics labeled for use on human or animal tissue are regulated as drugs under the Federal Food, Drug and Cosmetic Act. Whereas disinfectants are commonly associated with chemicals, the official definition of *disinfection* by the American Public Health Association (1950), U.S. Public Health Service, and British Ministry of Health includes physical agents as well: *Disinfection*—killing of pathogenic agents by chemical or physical means directly applied.

It is now about 60 years since Patterson made his study of the existing definitions of the word disinfectant. I have attempted to update Patterson's study by examining and analyzing the definitions given by 15 modern dictionaries: eight medical, two chemical, two legal, and three general. The results are given in Table 2–1. It will be noted that there are five elements in the definition of disinfection that have been given in the discussion above. These are that a disinfectant (1) removes infection, (2) kills, not just inhibits, microorganisms in the vegetative stage, (3) does not necessarily kill spores, (4) is ordinarily a chemical but can be a physical agent, and (5) is used only on inanimate objects, not on the human or animal body. It is important to make these distinctions if we are to distinguish the term disinfectant from other terms that follow, such as antiseptic, sporicide, and bacteriostat.

It will be noted from Table 2–1 that only one of the dictionaries, *Taber's Medical Dictionary*, contained all five elements of the definition. *Taber's* also was the only dictionary that specifically stated that a disinfectant could be chemical or physical. Others merely used the words "an agent" and were given credit in our table for either chemical or physical. All of the dictionaries perpetuated the oldest aspect of the definition, namely, freeing from infectious disease. *Black's Law Dictionary* defines disinfected as "Made free from injurious or contagious disease. Immunization." Injurious disease might be noninfectious diseases like arthritis or diabetes, and how immunization is equivalent to disinfection, only the writers of that dictionary can explain. *Taber's Medical Dictionary* states that a disinfectant prevents infection by killing bacteria. No mention of fungi, viruses, or protozoans. Some dictionaries use terminology such as "a disinfectant destroys, eliminates, neutralizes, or inhibits growth or activity of harmful microorganisms, or renders them inert." If it just inhibits or renders inert it would not be considered a disinfectant but a bacteriostatic, fungistatic, or other agent. The *Random House Dictionary* refers to a disinfectant as any chemical agent that destroys harmful organisms. That definition would include insecticides that kill malaria mosquitos, because they are harmful organisms. *Steadman's* includes the elimination of toxins or vectors as well as pathogenic microorganisms. Vectors might also include the malaria mosquitos.

Three dictionaries, *Steadman's*, *International*, and *Hawley's*, define "complete" and "incomplete disinfection." They state complete disinfection kills both vegetative organisms and spores, whereas incomplete disinfection kills only the vegetative form. These terms relate to "levels of disinfection" proposed by Spaulding (Lawrence and Block, 1968) for rating disinfectants used for medical instruments. He designated three levels of disinfection action: high-level which kill all microorganisms (sporicides); low-level, which kill only vegetative cells and some viruses; and intermediate-level, which kill vegetative cells, most viruses, and some spores. This system has been accepted by the Centers for Disease Control (Garner and Favero, 1985) in their guideline for "Cleaning, Disinfecting, and Sterilizing Patient Care Equipment." It is important, however, to use the term sterilization or sporicidal where all forms are killed and not to use disinfection or complete disinfection. The APIC (Association for Practitioners in Infection Control) proposed levels, which include sterilization, high-level disinfectant, and low-level disinfectant (Rutala, 1990), would therefore be preferred. Another definition, given by Random House, for disinfection is "to cleanse (clothing, wounds, etc.) to destroy harmful microorganisms." *Black's Medical* tells us that disinfection is the "process of rendering harmless any persons, articles, rooms, and the like which are liable to communicate disease." In today's understanding of the term we do not disinfect people or wounds. We treat them with antiseptics. The idea of cleaning goes hand-in-hand with disinfection, and the distinction may be confused. The legal dictionary, *Words and Phrases*, tells of a court case in which a company that disinfected a railroad for carrying food left it dirty and was sued. The judge explained that disinfection did not mean that all dirt had to be removed, as long as it did not contain living microorganisms capable of doing harm; thus the case was lost. Whereas the word disinfectant was originally and still is used primarily with regard to pathogenic microorganisms in a medical setting, the more general use would cover a range of nonmedical organisms and applications such as a toilet bowl disinfectant, water cooling-tower disinfectant, or drilling-mud disinfectant. It can be concluded from this analysis that dictionary definitions in this area can not be counted on for strict, modern meanings. They can be used as a beginning, but one would be better advised to consult professionals actively working in the field for more accurate, complete interpretation of the terms.

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000008

**Table 2–1.** *A Comparison of 15 Dictionaries on 5 Elements of the Definition of Disinfection*

| Criteria | Dorland's Medical *27th, 1988* *W.B. Saunders* | Gould's Medical *3rd, 1972* *McGraw-Hill* | Webster's Medical *1986* *Merriam-Webster* | Steadman's Medical *25th, 1990* *Williams & Wilkin* |
|---|---|---|---|---|
| 1. Removes infection | + | + | + | + |
| 2. Kills microorganisms | – | – | + | + |
| 3. May not kill spores | – | – | + | – |
| 4. May be chemical or physical | – | + | + | – |
| 5. Used only on inanimate objects | + | + | – | – |

| Criteria | Taber's Medical *16th, 1989* *F.A. Davis* | Mosby's Medical *3rd, 1990* *C.V. Mosby* | Black's Medical *35th, 1987* *Barnes & Noble* | International Medical & Biolog *1986* *Wiley* |
|---|---|---|---|---|
| 1. Removes infection | + | + | + | + |
| 2. Kills microorganisms | + | + | + | + |
| 3. May not kill spores | + | – | + | – |
| 4. May be chemical or physical | + | – | – | – |
| 5. Used only on inanimate objects | + | – | – | + |

| Criteria | Condensed Chemical *1961* *Rheinhold* | Hawley's Condensed Chemical *1987* *Van Nostrand-Rheinhold* | American Heritage General *1973* *Houghton Mifflin* | Random House General *1968* *Random House* |
|---|---|---|---|---|
| 1. Removes infection | + | + | + | + |
| 2. Kills microorganisms | + | + | – | + |
| 3. May not kill spores | + | + | – | – |
| 4. May be chemical or physical | – | – | + | – |
| 5. Used only on inanimate objects | + | + | + | – |

| Criteria | Oxford English General *2nd, 1989* *Oxford* | Black's Law *1954* *West* | Words & Phrases Law *1954* *West* |
|---|---|---|---|
| 1. Removes infection | + | + | + |
| 2. Kills microorganisms | + | – | + |
| 3. May not kill spores | – | – | – |
| 4. May be chemical or physical | – | – | – |
| 5. Used only on inanimate objects | – | – | – |

+ Includes this element of the definition
– Doesn't include this element of the definition

A chemical may have different antimicrobial designations depending on its application. For example, Fraser (1987) mentions a number of designations for peracetic acid: "It should be noted the terms used for disinfectants vary between industries, e.g., 'sanitizers' in food and brewing industries, 'terminal disinfectants' in dairies, 'biocides' in municipal water purification, 'ovicides' in agricultural waste stabilization, 'sterilants' in medicinal and pharmaceutical applications." Of course, peracetic acid may be bacteriostatic under certain conditions with short contact time, bactericidal with longer time, and sporicidal or biocidal with even longer time. Each is a proper designation for the conditions of use. On the other hand, some industries may employ terminology peculiar to that industry with no regard to properly accepted definitions. It would be desirable to have definitions accepted internationally but they a not; therefore there may be different interpretations the terms as they are used in different countries.

### *Antiseptic*

An antiseptic is a substance that prevents or arres the growth or action of microorganisms either by inhi iting their activity or by destroying them. The term used especially for preparations applied topically to livi tissue.

The legal definition (Federal Food, Drug and Co metic Act, 1938) states: The representation of a drug its labeling as an *antiseptic* shall be considered to be representation that it is a germicide, except in the ca of a drug purporting to be, or represented as, an *ant septic* for inhibitory use as a wet dressing, ointmen

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000009

dusting powder, or other such use as involves prolonged contact with the body. For a more complete definition and discussion of the use of the term antiseptic, refer to Chapter 58.

***Comments.*** The word "antiseptic," derived from the Greek "against putrefaction," was used by Pringle in 1750 (see Chapter 1) to record the ability of substances to prevent the spoilage of organic matter such as egg and meat. After Lister's research in the use of antimicrobial agents in surgery, the term acquired a second meaning, that of a substance used to destroy pathogenic microorganisms. There was some difference of opinion in regard to the second meaning—whether an antiseptic merely inhibited the growth of microorganisms, killed them, or both. Patterson examined 165 definitions of *antiseptic* used between 1819 and 1930, of which 20 make no mention of bacteria; 27 state that they arrest but do not destroy, 12 that they destroy, 10 that they inhibit growth but do not indicate how, 66 that they do one or the other, and 30 that antiseptics act to neutralize toxins, etc. A similar survey in 1921 shows that 37 of 53 citations described an antiseptic as inhibiting microorganisms without necessarily killing them, whereas only 6 held that they functioned by killing. The mode of action of course may depend upon such criteria as concentration used, time of contact, temperature, pH, nature of the organism, organic matter present, etc., and such conditions have been included in more restrictive definitions of many of these terms. For example, formerly under the Federal Food and Drug Act of 1938, mouthwashes, douches, and gargles that are allowed to remain in contact with the tissue for short periods were permitted to be labeled as antiseptics only if they destroy organisms in the dilutions recommended for use. Currently, the FDA (1974) specifies clinical verification of infection prevention.

### *Germicide*

A germicide is an agent that destroys microorganisms, especially pathogenic organisms.

***Comment.*** The word "germ" is a popular one and has been used to form the convenient term *germicide*, which finds extensive use in the technical as well as the popular literature. As commonly used, the term is associated with the death of all disease-producing microorganisms but, like the word disinfectant, to which it is similar, it does not necessarily include the capability of destroying bacterial spores. Since germicide is a popular term it is often misused to include sporicides, as in the phrase "high level germicides," which includes sporicides like ethylene oxide. It should be stated that usage eventually determines meaning and if a word is generally used in a certain way, its meaning will change to conform to its common use, regardless of authority's efforts to the contrary. This seems to be occurring with the term germicide. It applies to use on both living tissue and inanimate objects. It refers to chemical agents, but the adjective "germicidal" may refer to physical agents, as for example, *germicidal* lamps.

### *Bactericide*

A bactericide is an agent that kills bacteria.

***Comment.*** This term is applied to chemical agents that kill all bacteria, both pathogenic and nonpathogenic, but not necessarily bacterial spores. It is used for both living tissue and inanimate objects. It differs from *germicide* in that is does not include fungi, viruses, and other microorganisms that are not bacteria, although it may kill them but does not claim to do so.

### *Fungicide*

A fungicide is an agent that kills fungi.

***Comment.*** This term is associated with chemicals and includes substances applied to both living tissue and inanimate objects. Unlike the definition of *bactericide*, no mention is made to exclude spores; therefore, the assumption should be made that fungus spores are also killed.

### *Virucide*

A virucide is an agent that destroys or inactivates viruses, especially a chemical substance used on living tissue.

***Comment.*** The word virucide is a misnomer because the ending "cide" means kill and the virus, by itself, is not a living entity. Thus we do not say a virus is killed, but that a virus is inactivated. The spelling "viricide" is sometimes used but is not preferred.

### *Sporicide*

A sporicide is an agent that destroys microbial spores, especially a chemical substance that kills bacterial spores. The term is commonly used in reference to substances applied to inanimate objects. Because spores are more resistant than vegetative cells, a *sporicide* would be a sterilizing agent, killing such resistant forms as amoebic cysts.

### *Biocide*

A biocide is a substance that kills all living organisms, pathogenic and nonpathogenic.

***Comment.*** Because a *biocide* kills spores as well as vegetative cells, it is presumably a sterilizing agent. The definition includes all species of living organisms, micro and macro, but the term is commonly used with reference to microorganisms.

### *Bacteriostat*

A bacteriostat is an agent, usually chemical, that prevents the growth of bacteria but that does not necessarily kill them or their spores. Similarly, a *fungistat* and a *biostat* refer to the prevention of growth of fungi and of all living organisms, respectively. Sometimes the only difference as to whether a chemical is bacteriostatic or bactericidal depends on the conditions of application, such as time, temperature, or pH.

### *Fungitoxic*

An agent is termed *fungitoxic* that inhibits but does not necessarily kill fungi. It is equivalent to the term *fungistatic*.

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000010

### *Antibiotic*

An antibiotic is an organic chemical substance produced by microorganisms that has the capacity in dilute solutions to destroy or inhibit the growth of bacteria and other microorganisms, used most often at low concentrations in the treatment of infectious diseases of man, animals, and plants.

### *Sterilization*

Sterilization is the act or process, physical or chemical, that destroys or eliminates all forms of life, especially microorganisms.

***Comment.*** Because of the misuse of this term, the council on Pharmacy and Chemistry of the American Medical Association (1936) officially went on record stating that sterilization was intended to convey an absolute meaning, not a relative one. A substance cannot be partially sterile. Nevertheless, the word is still used in the partial sense, as noted by Lawrence (1968), for mechanically filtered solutions called "sterile" although, while being free of bacteria and fungi and their spores, they may contain active viruses that are not removed by the filter.

Because it cannot be known with certainty whether all microorganisms of all types have been killed because we may not even be aware of the existence of some species or have media suitable for culturing all organisms, and furthermore, because we can never prove the achievement of a negative absolute (species once claimed to be extinct occasionally turn up), it becomes more practical, as pointed out by Bruch and Bruch (1971), to employ a process definition of sterilization. By this definition, sterilization is the process by which living organisms are removed or killed to the extent that they are no longer detectable in standard culture media in which they previously have been found to proliferate. According to this definition, both the process used to achieve sterility and the methods for testing for it are equally important.

Microorganisms of the same species vary in their resistance to chemical and physical agents, and if even one of a billion organisms survives, there is the possibility of rapid multiplication and contamination of the material. Although, as stated, the term sterile implies an absolute, in practice it becomes a matter of probability whether sterility has been achieved. Different operations require different degrees of certainty of sterility, as measured by the percent reduction or number of logarithmic reductions (D values) in initial count brought about by the treatment.

### *Criteria of Sterilization*

***Thermal Death Time.*** The time required to kill all spores at a specified temperature.

***D Value, $D_{10}$ Value, or Decimal Reduction Time (DRT).*** This value is defined as the time required to inactivate 90% of the cells present or to reduce the microbial population to one-tenth its number, that is, a one-logarithm reduction.

***F Value.*** The F value is the time in minutes required to kill all the spores in suspension when at a temperature of 121° C or 250° F.

***Z Value.*** The Z value is a measure of the way the D value changes with temperature for a particular organism. It may be considered the slope of the logarithm of the thermal death time against temperature. Mathematically, it is defined:

$$Z = \frac{T_2 - T_1}{\log\left(\frac{D_2}{D_1}\right)},$$

where T is in °F.

***$Q_{10}$ Value.*** Like the Z value, the $Q_{10}$ value is also a measure of inactivation rate with temperature. It is defined as the ratio of inactivation rate constants at two temperatures 10° C apart.

### *Sanitizer*

A sanitizer is an agent that reduces the number of bacterial contaminants to safe levels as judged by public health requirements. It is commonly used with substances that are applied to inanimate objects.

***Comment.*** This term is associated with the cleaning of eating and drinking utensils and dairy equipment and is restricted to cleaning operations, as in the case of a *detergent sanitizer*, which combines both cleaning and antibacterial properties. According to the official sanitizer test (See Chapter 60), a sanitizer is a chemical that kills 99.999% of the specific test bacteria in 30 seconds under the conditions of the test.

### *Prophylactic*

A prophylactic agent is one that contributes to the prevention of infection and disease.

***Comment.*** This word is wide in scope. It is used for rubber condoms and antiseptic lotions and may even refer to fresh air and a nutritious diet when these serve to ward off disease.

### *Preservation*

Preservation is the process by which chemical or physical agents prevent biologic deterioration of materials.

### *Biologic Indicator*

A biologic indicator (BI) is a preparation of microorganisms, usually bacterial spores, that is carried either directly by some of the items to be sterilized or by adventitious carriers such as filter paper, threads, and porcelain cylinders, and that serves as a challenge to the efficiency of a given sterilization process or cycle.

### *Soaps and Skin Preparations*

Several additional terms to receive formal definition (OTC Antimicrobial I Drug Review Panel, 1974) relate to antimicrobial substances for application to the skin:

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000011

***Antimicrobial Soap:*** A soap containing an active ingredient with in-vitro and in-vivo activity against skin microorganisms.

***Health-Care Personnel Handwash:*** A safe, nonirritating preparation designed for frequent use that reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying. If the preparation contains an antimicrobial agent, it should be broad spectrum, fast acting, and, if possible, persistent.

***Patient Preoperative Skin Preparation:*** A safe, fast-acting, broad-spectrum antimicrobial-containing preparation that significantly reduces the number of microorganisms on intact skin.

***Skin Antiseptic:*** A safe, nonirritating, antimicrobial-containing preparation that prevents overt skin infection. Claims stating or implying an effect against microorganisms must be supported by controlled human studies that demonstrate prevention of infection.

***Skin Wound Cleanser:*** A safe, nonirritating liquid preparation (or product to be used with water) that assists in the removal of foreign material from small superficial wounds and does not delay wound healing.

***Skin Wound Protectant:*** A safe, nonirritating preparation applied to small cleansed wounds that provides a protective (physical and/or chemical) barrier and neither delays healing nor favors the growth of microorganisms.

***Surgical Hand Scrub:*** A safe, nonirritating, antimicrobial-containing preparation that significantly reduces the number of microorganisms on the intact skin. A surgical hand scrub should be broad spectrum, fast acting, and persistent.

### *Some Other Words*

***Algicide:*** A substance that kills algae; unicellular chlorophyll-containing plants.

***Antimicrobial Agent:*** Any agent that kills or suppresses the growth of microorganisms.

***Asepsis:*** Prevention from contamination with microorganisms. Includes sterile conditions in tissues, on materials, and in rooms, as obtained by exclusion, removing, or killing organisms.

***Bioburden:*** The excess microbiologic load, that is, the number of contaminating organisms in the product prior to sterilization. For example, it will be more difficult to sterilize a product heavily loaded with spores than one lightly loaded.

***Biodeterioration:*** The deterioration of valuable materials due to biological activity. The vectors are usually microbiological but may be insects, rodents, or higher animals or plants. Deterioration may be due to the breakdown of the material, biodegeneration, as in decay of timber, or it may be due to aesthetic depreciation, as in staining of works of art.

***Chemisterilant:*** A chemical used to kill all microorganisms, including spores.

***Chemitherapeutant:*** A chemical used inside the body that kills or suppresses microorganisms to control disease, as for example, quinine taken for malaria control or sulfadrugs for various microbial diseases.

***Contamination:*** The introduction of microorganisms into tissues or sterile materials.

***Decontamination:*** Disinfection or sterilization of infected articles to make them suitable for use.

***Degerming Agent:*** A disinfecting agent.

***Disinfestation:*** Extermination or destruction of insects, rodents, or other animal forms that transmit disease, which may be on a person, his belongings, his clothing, or his surroundings.

***Fumigation:*** Exposure of an area or object to disinfecting fumes.

***Inactivation:*** Removal of the activity of microorganisms by killing or inhibiting reproduction or enzyme activity. When referring to an antimicrobial agent, inactivation means neutralizing its activity by any means.

***Ovicide:*** A substance that kills the eggs of very small infectious animals, such as the eggs of tapeworms.

***Pasteurization:*** A process developed by Louis Pasteur of heating milk, wine, or other liquids to around 60°C for about 30 minutes to significantly reduce or kill the number of pathogenic and spoilage organisms.

***Pathogen:*** Any disease-producing microorganism. In current circumstances in which drugs, radiation, or AIDS may cause immunosuppression, the distinction between pathogens and nonpathogens may no longer be significant.

***Planktonic:*** Describes growth of microbiological organisms dispersed in solution, as in the case of free-swimming plankton.

***Prions:*** Little-understood virus-like infectious agents that cause serious diseases of man and animals. Prions are thought to differ from viruses by containing neither DNA or RNA, only protein. They are extremely resistant to inactivation by heat and disinfecting agents.

***Sessile:*** Describes growth of microorganisms growing attached to a body, not freely dispersed in planktonic growth.

***Tyndallization:*** A process of heat treatment for killing microorganisms by which the treated material is heated to less than sterilization temperatures then allowed to cool and stand to incubate any spores that would germinate. This process is successively repeated for several days to destroy all vegetative forms and germinated spores.

***Viroids:*** Virus-like infectious agents that produce diseases in higher plants. They differ from true viruses in that they are believed to contain no protein, only low-molecular-weight ribonucleic acid.

### *Origin of Terms*

It might be of interest to examine the origin of a few of the terms we use now that we have considered their meanings. One will find that the terms follow closely the history of disinfection, which is presented in Chapter 1. Some are as old as the English language; others are quite recent. The word disinfectant was first recorded in writing in 1598, with the meaning "to cure, to heale," but

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000012

in 1658 it was used in the more modern sense, to remove infection: "They use to make great fires, where there is household stuffe of men that died of the Pestilence to dis-infect them." (See the *Oxford English Dictionary*, OED, 1989, for references to quotations in this section.) In those days it was believed that contagious diseases arose from effluvia, a flowing-out of invisible particles from the diseased person or corpse, or from miasmas, which were noxious disease-bearing exhalarations from putrefying organic matter emanating from damp, unhealthful places like malarial swamps. Miasmas were referred to in medical writing as early as 1665. The word *disease*, coming from the French, meaning absence of ease, or discomfort, appeared in English about 1330 and was used by Chaucer in 1386. Chaucer was aware of the spread of infection by such means as coughing, for in 1386 he wrote, "Hoold cloos thy mouth . . . Thy cursed breeth infecte wole us alle." (Hold closed your mouth . . . your cursed breath will infect us all.) The word *antiseptic* is credited to John Pringle, whose experiments in 1750 are described in Chapter 1. He was familiar with the word *septic*, first recorded in 1605, which means putrefying. As a physician, he had written "The miasma or septic ferment being received into the blood," and when he found chemicals that prevented putrefaction, the word *antiseptic* was generated.

Although Leeuwenhoek first saw bacteria in 1676, the term was not recorded in use until 1847 to 1849. Leeuwenhoek just referred to "the little animals" or, in English, *animalcules*, a term first recorded in 1599 to refer to any small animal and in 1677 to mean those seen only under the microscope. It should be recognized that the terms discussed in this section may have been in oral use much earlier, but the written record gives the only dates that can be depended upon. After bacteria, we find Tyndall using the adjective *bactericidal* in 1878; *bactericide* follows in 1884, the year that the word *bacteriology* appeared: "Permanganate of potash is not a bactericide of great activity," but by 1894 we see that "A solution of formaldehyde appears to be a very powerful bactericide."

The familiar word *microbe* did not arise by spontaneous generation, despite the strong belief by many respectable scientists in that mechanism of origin of microorganisms. It was the invention of the French surgeon, Charles Sédillot, an admirer of Pasteur and one of the first French physicians to apply Lister's antiseptic method. He wanted a word that would include bacteria and all the other tiny organisms that could be seen only with the microscope. The philologists criticized the word because its Greek root suggested an animal with a short life rather than an infinitesimally small animal. But with terminology for the tiny creatures in an uncertain state, with terms like *bacteridites* being used, Pasteur adopted the term and it was accepted worldwide. It was in 1878 that Sédillot presented his paper with the new word. By 1880 we had *microorganism*, by 1885 *microbiologist* and *microbiocide* in *Science* and *The British Medical Journal*, respectively, and the field of *microbiology* in 1888 in *Popular Science Monthly*. The adjective *microbiocid* didn't arrive until 1897.

The word *fungus* goes back much further, becaus mushrooms and other fungi didn't require a microscop to be seen. Fungus, spelled *fungous*, first appeared i the English language in 1420 and was used as a huma infection in 1674 to 1677. The word *fungicide*, howeve didn't show up until 1889, when it appeared in *The Voic* a New York City newspaper. It is probable that earlie use in technical publications was not uncovered by th OED researchers. As in the case of *bactericidal*, th adjective *germicidal*, in a medical journal, preceded i 1880 the noun *germicide*, in 1881, in the London *Time* The word *germ*, in relation to a smallpox infection, wa printed in 1803. *Germifuge* is listed in one medical di tionary as an obsolete term for disinfectant, but I coul find no reference to its actual use.

In reading an article on disinfection written in the earl 1800s I was surprised to see the word *virus* used i connection with a disease. This was many years befor bacteria were known to cause disease, and viruses coul not even have been seen with the microscope. On lool ing into the matter I discovered that virus was the Lati word for poison and was used, as such, as early as 159 Its use eventually became more restricted to a substanc related to contagious disease, as in the 1728 descriptio "a corrosive or contagious pus." In 1880 Pasteur state "The virus is a microscopic parasite which may be mu tiplied by cultivation outside the body of an animal." Th adjective *virucidal* was first noted in 1925, and to ou surprise the OED does not contain the word *virucid* The term *biocide*, to mean destruction of tissues of th human, was first recorded in 1947, and in 1963 Rach Carson used biocide in her book *Silent Spring* to mea "genocide." In 1968, at a biodeterioration symposiu it was finally used in the way we define it, as referri principally to microorganisms, being a sterilizing agen *Sterilization*, as in "Sterilization by heat or organic li uids," was written in 1874, but the word *sterile* did n appear until 1877; in 1891 the steam *sterilizer* was me tioned in print. *Antibiotic* did not come into use un after penicillin, appearing in *Lancet* in 1944. The ter *sanitizer* appeared first in the *Journal of Milk and Foo Technology* in 1950. The second mention of *sanitiz* listed by the OED was in 1968 and referred to the fir edition of this book, where Chapter 4 gave methods f testing sanitizers and bacteriostatic substances. Thu this book not only records the history of disinfection b itself has become part of that history.

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SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000013

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SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000014

CHAPTER 13

# QUATERNARY AMMONIUM ANTIMICROBIAL COMPOUNDS

John J. Merianos

The quaternary nitrogen moiety is an essential component for many biologically active compounds. Quaternary ammonium compounds play an important role in the living process. From vitamins (vitamin B complex and thiamine) to enzymes carboxylase, which participates in the carbohydrate metabolism, to choline, which is involved in transmethylation reaction of the fat metabolism, and to acetylcholine, a mediator in the transmission of nerve impulses (Burger, 1960), all play a fundamental function.

There are at least four types of physiologic actions (Burger, 1960) associated with quaternary ammonium compounds: (1) Curare-like (curaremimetic or curareform) action, a muscular paralysis with no involvement of central nervous system or heart, produced by d-tubocurarine chloride used to induce muscular relaxation during surgery; (2) muscarinic-nicotinic action, which is a direct stimulation of smooth muscles, and is a primary transient stimulation and secondary persistent depression of sympathetic and parasympathetic ganglia; (3) ganglia-blocking action; and (4) neuromuscular blockade. Table 13–1 illustrates the chemical structures of representative compounds responsible for these physiologic actions.

Medicinal chemists using the principle of structure activity relationships (Goldstein, 1974) have synthesized many quaternary ammonium compounds that will mimic certain biologic effects. Thus a very complex structure of d-tubocurarine chloride can be reduced to a much simpler decamethonium structure, a neuromuscular blocking agent. Hexamethonium acts as a ganglionic blocker by preventing the receptor from responding to acetylcholine. The decamethonium is too long to fit the ganglionic receptor but would act as a neuromuscular blocker by preventing the combination of acetylcholine with muscle end plate receptors. When the number of carbon atoms separating the quaternary nitrogens is increased above 12 carbons, the autonomic nervous activity disappears and the compounds become surface active and antimicrobial. However, there are exceptions to this rule, as we will discuss later on in the case of bis-quaternary and polymeric quaternary ammonium compounds, where two and four carbon atoms separate the quaternary nitrogen, and the products have antimicrobial properties. This chapter is concerned exclusively with antimicrobial quaternary ammonium compounds.

## DISCUSSION

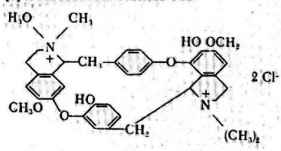
Although there are many stages in the historical development of quaternary ammonium germicides, there is general agreement on at least two truly historical milestones. The first is the work of Jacobs et al., which examined structure, preparation, and antimicrobial activity. Jacobs and Heidelberger, in 1915, published a number of papers describing the preparation of various different series of the quaternary ammonium salts of hexamethylenetetramine. In 1916 Jacobs and his coworkers published three papers describing the antimicrobial activity of many of the quaternary ammonium compounds they had previously synthesized and of additional derivatives prepared therefrom. In these publications, they related structure to antimicrobial activity. Although some reviews have challenged the work of Jacobs et al. as the earliest investigations of quaternary ammonium germicides, their preeminence is assured by their quality, quantity, and treatment, which included antimicrobial activity and correlation between structure and antimicrobial activity. The only valid criticism of the work of Jacobs may be the fact that some of the antimicrobial activity of his products may be due to the release of formaldehyde from hexamethylenetetramine. Jacobs reported that the antimicrobial activity is due to the presence of hexamethylenetetramine nucleus. Methenamine mandelate USP is used as a urinary tract anti-infective



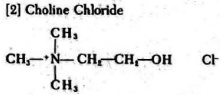
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EXHIBIT 1023 PAGE 000015

**Table 13–1.** *Quaternary Structures with Physiological Actions*

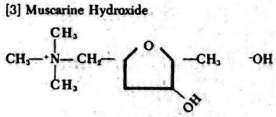
[1] d-Tubocurarine Chloride USP



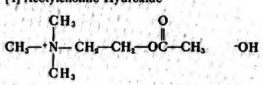
[2] Choline Chloride



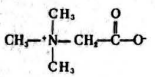
[3] Muscarine Hydroxide



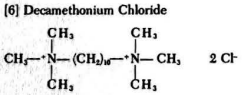
[4] Acetylcholine Hydroxide



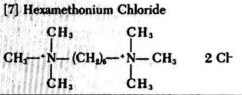
[5] Betaine



[6] Decamethonium Chloride



[7] Hexamethonium Chloride



even today, acting by releasing formaldehyde in an acid medium (Gennaro, 1985).

In any consideration of earlier investigations, the reader is reminded that our interests are solely with the various aspects of the antimicrobial activity of the quaternary ammonium compounds. Consequently, we may exclude those early publications dealing completely with synthesis of these compounds and in addition refute the role attributed by other reviews to the nineteenth century research on curare (Cucci, 1949).

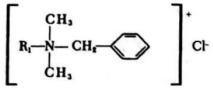
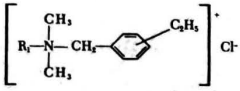
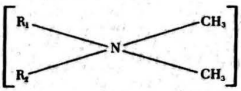
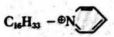
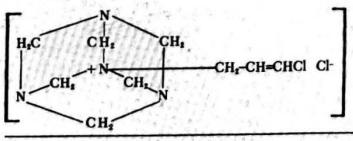
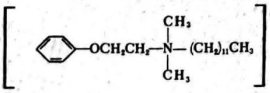
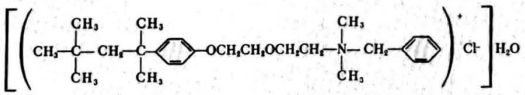
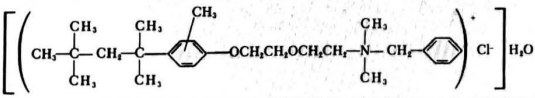
Not until the 1920s did any additional information appear, at which time Browning et al. (1922, 1926) and Browning (1926) described the bacterial activity of quaternary derivatives of pyridine, quinoline, and other ring structures. Hartmann and Kagi, in 1928, reported on the antibacterial activity of quaternary ammonium compounds of acylated alkylene diamines. It was not until 1935, when Domagk disclosed the antibacterial activity of the long-chain quaternary ammonium salts, that the second and most important milestone in the development of antimicrobial quaternary ammonium compounds took place. The improved germicidal activity that occurred when a large aliphatic residue was attached to the quaternary nitrogen atom established the practicability and utility of these compounds, first in medicine and later in many other applications. This important disclosure stimulated research in synthesis and antimicrobial testing of quaternary ammonium compounds, with the consequent frequent publications and patents issued from 1935 to the present. After Domagk's discovery of the biocidal properties of cationic surface active agents several generations of structurally variable quaternary ammonium antimicrobials of commercial importance were developed.

The first generation is the standard benzalkonium chloride of specific alkyl distribution, namely $C_{12}$—40%, $C_{14}$—50%, $C_{16}$—10%. Another version of equally commercially successful alkyl distribution in the benzalkonium series is $C_{12}$—5%, $C_{14}$—60%, $C_{16}$—30%, $C_{18}$—5% as shown in Table 13–2. The official United States Pharmacopeia recognizes the benzalkonium chloride as a pharmaceutical aid (antimicrobial preservative). The USP specification for the $C_{12}/C_{14}$ homologs components is 70% minimum of the total alkylbenzyldimethyl ammonium chloride content. This broad specification does not always give the most efficacious product. The major determining factor for biocidal efficacy is the hydrophilic-lipophilic balance of the products. The peak for biocidal activity of the homolog series is illustrated on Table 13–3, with a carbon chain of 14 offering the best activity (Cutler et al., 1966; Daoud et al., 1983; Hansch et al., 1973, 1964; Lien et al., 1976, 1968).

Modifications in the first-generation quaternaries by substitution of the aromatic ring hydrogen with chlorine, methyl, and ethyl groups resulted in the second generation of the substituted benzalkonium compounds. Out

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000016

**Table 13–2.** *Commercial Antimicrobial Quaternary Ammonium Compounds*

| *Chemical Structure* | *Trade Names* | *Manufacturers* |
|---|---|---|
| **Benzalkonium Chlorides:** | | |
|  | BTC 835, BTC 824 | Stepan (Onyx) |
| | BTC 50 USP | " |
| | Barquat MB-50 | Lonza |
| | Variquat 50 MC | Sherex |
| | Zephiran Chloride | Winthrop |
| | Hyamine 3500 | Lonza |
| $R_1$ = $C_{12}$—40%, $C_{14}$—50%, $C_{16}$—10% | Maquat MC 1412 | Mason |
| $R_1$ = $C_{12}$—5%, $C_{14}$—60%, $C_{16}$—30%, $C_{18}$—5% | Maquat MC 1416 | Mason |
| **Substituted Benzalkonium Chlorides:*** | | |
|  | BTC 471 | Stepan (Onyx) |
| | BTC 2125M | " |
| | Barquat 4250 | Lonza |
| | Maquat MQ-2525M | Mason |
| $R_2$ = $C_{12}$—50%, $C_{14}$—30%, $C_{16}$—17%, $C_{18}$—3% | | |
| $R_2$ = $C_{12}$—68%, $C_{14}$—32% | | |
| *See Text and Brochures | | |
| **Twin Chain Quaternaries:** | | |
|  | BTC 818, BTC 812 | Stepan (Onyx) |
| | BTC 1010 | " |
| | Bardac 2050 | Lonza |
| | Bardac 205M | " |
| | Bardac 2250 | " |
| Dioctyl 25%, Didecyl 25%, Octyldecyl 50% | | |
| $R_1$ = Octyl, $R_2$ = Dodecyl | | |
| **Cetylpyridinium Chloride:** | | |
|  | Cepacol Chloride | Merrell Labs. |
| | Ceepryn Chloride | " |
| **N-(3-Chloroallyl)Hexaminium Chloride:** | | |
|  | Dowicide Q | Dow |
| | Dowicil 200 | Dow |
| | Dowicil 75 | Dow |
| **Domiphen Bromide:** | | |
|  | Bradosol | Proctor & Gamble |
| | Oradol | Ciba |
| | Modicare | " |
| **Benzethonium Chloride:** | | |
|  | Phemerol Chloride | Parke-Davis |
| | Hyamine 1622 | Rohm & Haas |
| | | Lonza |
| **Methylbenzethonium Chloride:** | | |
|  | Diaparene Chloride | Rohm & Haas |
| | Hyamine 10X | Rohm & Haas |

SALVACION: IPR2024-00711
EXHIBIT 1023 PAGE 000017

**Table 13–3.** *Effect of Length of Carbon Chain on Bactericidal Activity of Benzalkonium Chloride*

| | Bactericidal Test (Minimum Concentration That Kills in 10 Minutes but Not in 5 Minutes in ppm) | | |
|---|---|---|---|
| *Long-Chain Length* | *Staphylococcus aureus #6538* | *Salmonella typhosa #6539* | *Pseudomonas aeruginosa #15,442* |
| 8 | 3000 | 4500 | 6000 |
| 9 | 800 | 1400 | 2500 |
| 10 | 450 | 300 | 1200 |
| 11 | 160 | 130 | 400 |
| 12 | 45 | 40 | 120 |
| 13 | 25 | 20 | 50 |
| 14 | 15 | 12 | 40 |
| 15 | 25 | 20 | 70 |
| 16 | 30 | 25 | 200 |
| 17 | 170 | 15 | 360 |
| 18 | 450 | 60 | 1000 |
| 19 | 330 | 90 | 1300 |

of this group the product with commercial significance is the alkyldimethylethylbenzyl ammonium chloride under the trade name BTC 471 with alkyl distribution $C_{12}$—50%, $C_{14}$—30%, $C_{16}$—17%, $C_{18}$—3%. Another product with high biocidal activity in this group is alkyldimethyl-3,4-dichlorobenzyl ammonium chloride under the trade names of Tetrosan 3,4D, and Riseptin with same alkyl distribution as above.

By far the product of greatest commercial significance today is of the third generation of quaternary ammonium compounds, the *dual quats*, developed in 1955 under the trade name BTC 2125M. This product is a mixture of equal proportions of alkyldimethylbenzyl ammonium and alkyldimethylethylbenzyl ammonium chlorides of specific alkyl distribution, as shown in Table 13–2.

This combination of benzalkonium chloride with alkyl distribution ($C_{12}$—5%, $C_{14}$—60%, $C_{16}$—30%, $C_{18}$—5%) and alkyldimethylethylbenzyl ammonium chloride with alkyl distribution ($C_{12}$—68%, $C_{14}$—32%) is BTC 2125M, with superior microbiologic performance (Onyx or Stepan brochures). This synergistic combination of the third generation of quaternaries not only had an increased biocidal activity, it reduced the acute oral $LD_{50}$ from 0.3 g/kg of benzalkonium chloride to an acute oral $LD_{50}$ of 0.750 g/kg for BTC 2125M.

In summary, the third generation—the dual quats—offer improved biocidal activity, stronger detergency, and a relatively lower level of toxicity. In the early 1950s the nonionic detergents were being developed with far greater cleaning power than natural soaps. The compatibility of quaternary ammonium compounds with nonionic detergents resulted in superior formulations that helped overcome the environmental factors, such as hard water, anionic residues of soap, and proteinaceous soils, which were found to weaken their effectiveness (Greene and Petrocci, 1980).

A continual change and improvement in advancing and broadening the spectrum of biocidal activity enabled disinfectants to work under the most adverse conditions and produced safer, more economical products. In 1965 another technological development, catalytic amination of long-chain alcohols, made commercially feasible the production of dialkylmethyl amines, which in turn can be quaternized with methyl chloride to give us the *twin chain quats*, the fourth generation of quaternaries antimicrobials with high performance, unusual properties, and tolerances (Ditoro, 1969; Petrocci et al., 1974). The twin chain quats, like dioctyl dimethyl ammonium bromide and didecyldimethyl ammonium bromide were first introduced by the British Hydrological Corporation (BHC, 1947. "DECIQUAM 222") for the British food industry.

These products displayed outstanding germicidal performance; unusual tolerance for anionic surfactants, protein loads, and hard water; and even low-foaming characteristics. Table 13–4 illustrates the cidal activities and pseudomonicidal, fungicidal, and hard-water tolerance of five of the most active twin chain quats, out of 20 as measured by the official AOAC procedure reported by Petrocci et al. (1974). The product of choice in this series is $C_9/C_{12}$DMAC because of its superior water solubility and germicidal activity. However, the odd number chain $C_9/C_{11}$DMAC is an equally active product, although its commercial feasibility has not been explored because of high cost of the odd carbon chain alcohols. Recently several odd carbon chain alcohols have been offered in semicommercial quantities. The concept of synergistic

**Table 13–4.** *Antimicrobial Activity of Twin-Chain Quaternary Ammonium Compounds*

| *Compounds* | *Pseudomonicidal* | *Fungicidal* | *HWT* |
|---|---|---|---|
| 1. $C_{10}/C_{16}$DMAC | 500 PPM | 210 PPM | 1100 PPM |
| 2. $C_8/C_{12}$DMAC | 500 PPM | 200 PPM | 1200 PPM |
| 3. $C_9/C_{11}$DMAC | 500 PPM | 190 PPM | 1400 PPM |
| 4. $C_8/C_{14}$DMAC | 550 PPM | 235 PPM | 1300 PPM |
| 5. $C_{10}/C_{11}$DMAC | 550 PPM | 210 PPM | 1300 PPM |

HWT = Hard Water Tolerance; DMAC = Dimethylammonium Chloride

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EXHIBIT 1023 PAGE 000018