

69667/87

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

597626

APPLICATION FOR A STANDARD PATENT

☒ We

SUTTON LABORATORIES, INC.
of 116 Summit Avenue,
New Jersey 07928,
UNITED STATES OF AMERICA.

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 19-2-90

hereby apply for the grant of a Standard Patent for an invention entitled:

"PRESERVATIVE COMPOSITIONS AND USES THEREOF"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
836,130	UNITED STATES OF AMERICA	4th March 1986

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 4th day of March 1987

To: THE COMMISSIONER OF PATENTS

H. M. Rimington

.....
(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention
entitled: "PRESERVATIVE COMPOSITIONS AND USES THEREOF"

Insert full name(s) and address(es)
of declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

I William E. Rosen
~~xxx~~ of
SUTTON LABORATORIES, INC., a corporation
existing under the laws of New Jersey;
116 Summit Avenue, Chatham, New Jersey
07928, United States of America

Cross out whichever of paragraphs
1(a) or 1(b) does not apply
1(a) relates to application made
by individual(s)
1(b) relates to application made
by company; insert name of
applicant company.

do solemnly and sincerely declare as follows :-

1. ~~xxxxxx I am xxxxxxxx~~
~~xxxxxx We are xxxxxxxx~~

or (b) I am authorized by

SUTTON LABORATORIES, INC.

Cross out whichever of paragraphs
2(a) or 2(b) does not apply
2(a) relates to application made
by inventor(s)
2(b) relates to application made
by company(s) or person(s) who
are not inventor(s); insert full
name(s) and address(es) of inven-
tors.

the applicant..... for the patent to make this declaration on ^{its} ~~their~~ behalf.

2. ~~xxxxxx I am xxxxxxxx~~
~~xxxxxx We are xxxxxxxx~~

or (b) BERKE, Philip A., of 95 Green Avenue, Madison,
New Jersey 07940, United States of America

ROSEN, William E., of 86 Canoe Brook Parkway,
Summit, New Jersey 07901, United States of
America

State manner in which applicant(s)
derive title from inventor(s)

~~xxx~~ the actual inventor.....^S of the invention and the facts upon which the applicant.....
~~are~~ is
~~is~~ entitled to make the application are as follows :-

An Assignment dated 4 March 1986 whereby the
actual inventors assigned the invention to
the said applicant

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications,
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ^{was} ~~xxxx~~ made
in The United States of on the 4 March 1986
by Philip A. Berke and William E. Rosen
in on the
by
in on the
by

4. The basic application..... referred to in paragraph 3 of this Declaration ^{was} ~~xxxx~~
the first application..... made in a Convention country in respect of the invention the subject
of the application.

Insert place and date of signature.

Declared at Chatham, NJ this 30th day of April 1987

Signature of declarant(s) (no
attestation required)

SUTTON LABORATORIES, INC.

Note Initial all alterations.

William E. Rosen
William E. Rosen, Executive V. Pres.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-69667/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 597626

(54) Title
BIOCIDAL COMPOSITION OF A HYDROXYMETHYLAMINOACETIC ACID AND AN ISO
THIAZOLIN-3-ONE DERIVATIVE

International Patent Classification(s)
(51)⁴ A01N 037/02 A01N 043/80

(21) Application No. : 69667/87 (22) Application Date : 04.03.87

(30) Priority Data

(31) Number (32) Date (33) Country
836130 04.03.86 US UNITED STATES OF AMERICA

(43) Publication Date : 10.09.87

(44) Publication Date of Accepted Application : 07.06.90

(71) Applicant(s)
SUTTON LABORATORIES, INC.

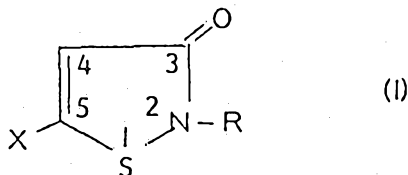
(72) Inventor(s)
PHILIP A. BERKE

(74) Attorney or Agent
DAVIES & COLLISON, MELBOURNE

(56) Prior Art Documents
US 4337269

(57) Claim

1. A ^{biocidal and antimicrobial composition} ~~composition of matter~~ comprising (i) a compound selected from the group consisting of hydroxymethylaminoacetic acid, its salts and its lower alkyl esters and (ii) one or more compounds of the formula (i):



wherein R is a lower alkyl group and X is hydrogen or a halogen.

8. A method for inhibiting microbial growth in a substance requiring microbial inhibition comprising incorporating into the substance an effective microbial growth inhibiting amount of composition of any one of claims 1, 2, 3, 4, 5, 6 or 7.

9. A preserved product comprising an effective microbial growth inhibiting amount of the composition of any one of claims 1, 2, 3, 4, 5, 6 or 7.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

COMPLETE SPECIFICATION

597626

(Original)

FOR OFFICE USE

Class

Int. Class

Application Number:
Lodged:

69667/87

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the
amendments made under
Section 49.

and is correct for printing.

Name of Applicant: SUTTON LABORATORIES, INC.

Address of Applicant: 116 Summit Avenue,
New Jersey 07928,
UNITED STATES OF AMERICA.

Actual Inventor(s): Philip A. BERKE

Address for Service: DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000.

Complete Specification for the invention entitled:

"PRESERVATIVE COMPOSITIONS AND USES THEREOF"

The following statement is a full description of this invention,
including the best method of performing it known to us :-

PRESERVATIVE COMPOSITIONS AND USES THEREOF

BACKGROUND OF THE INVENTION

Technical Field of the Invention

This invention is directed to compositions of matter containing a hydroxymethylaminoacetic acid derivative and one or more 3-isothiazolone compounds and their use to kill microorganisms and to inhibit microbial growth.

Description of the Prior Art

Hydroxymethylaminoacetic acid, its salts and lower alkyl esters, are known to be effective antimicrobial agents. Sodium hydroxymethylaminoacetate (CTFA Adopted Name: Sodium Hydroxymethylglycinate) is the active ingredient in the antimicrobial product marketed under the trademark Suttocide^(R) A.

United States Patents 4,105,431 and 4,252,694, disclose a group of compounds generally referred to as 3-isothiazolones, having biocidal properties. Kathon^(R) is the trademark for a family of biocides containing these compounds as active ingredients. More specifically, the Kathon^(R) biocides contain an aqueous mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in various weight ratios between about 2:1 and 4:1, respectively, with magnesium salts added as stabilizers. Kathon^(R) formulations have been proposed by the manufacturer for use as a biocide in various industrial applications, such as in cooling-tower water, metalworking fluids, latex emulsions and for slime control in paper mills. They have also been proposed as a biocide for swimming pool water and as an antimicrobial

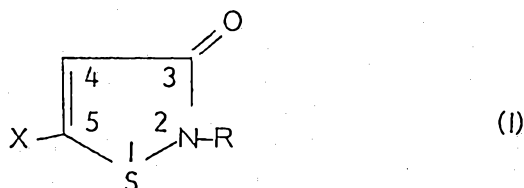
preservative for toiletries, cosmetics and household cleaning products. However, a significant drawback to the 3-isothiazolone compounds is their high toxicity, particularly their high corrosiveness and skin sensitizing properties.

SUMMARY OF THE INVENTION

We have discovered that the combination of a hydroxymethylaminoacetic acid derivative with one or more biocidal 3-isothiazolones exhibits synergistic biocidal and antimicrobial activity against a wide range of microorganisms.

The synergistic combination has a wide range of applications, including all areas where the Kathon^(R) family of biocides and preservatives are currently employed. The synergistic combination, advantageously, provides greater effectiveness, reduced costs and lower toxicological exposure of workers and consumers to the severe skin sensitizing properties of the 3-isothiazolones.

Accordingly, it is a primary object of the invention to provide a ~~biocidal and antimicrobial composition~~ ^{composition of matter} comprising (i) hydroxymethylaminoacetic acid, its salts or lower alkyl esters and (ii) one or more compounds of the formula (I):



wherein R is a lower alkyl group, preferably methyl, and X is hydrogen or a halogen, preferably chlorine. By incorporating an effective amount of this composition into a substance requiring microbial inhibition, the substance can be protected against a variety of microorganisms including bacteria, yeast and mold.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

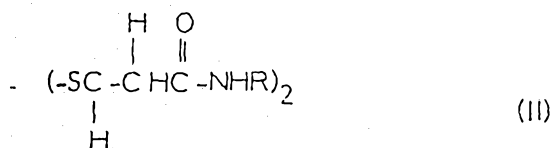
The hydroxymethylaminoacetic acid component of the composition of the invention is prepared as described in U.S. Patent 4,337,269, the disclosure of which is hereby incorporated by reference. As described therein, in preparing this component, a mixture of glycine and a basic reagent, such as an



alkali metal hydroxide, is prepared and mixed with formaldehyde in a molar ratio of glycine to formaldehyde of about 1:1. To obtain a salt other than the alkali metal salt, a compound which will cause replacement of the alkali metal cation is added to the reaction mixture. In this manner, numerous salts can be prepared including aluminum hydroxymethylaminoacetate, calcium hydroxymethylaminoacetate, magnesium hydroxymethylaminoacetate, copper hydroxymethylaminoacetate and zinc hydroxymethylaminoacetate. When alkyl glycinates are reacted in place of glycine, alkyl hydroxymethylaminoacetates are produced. Of these esters, lower alkyl esters, e.g., methyl hydroxymethylaminoacetate are most preferred.

After the reaction is complete, an equilibrium mixture of reaction products is obtained as a relatively clear, aqueous solution. The final form of the product may be a solution or a crystalline powder which is readily dissolved in aqueous media.

The 3-isothiazolones used in the composition of the invention are prepared as described in the previously cited U.S. Patents 4,252,694 and 4,105,431, the disclosures of which are hereby incorporated by reference. As described therein, these compounds can be prepared by the cyclization of a substituted disulfide-amide having the formula (II):



where R is as previously defined. The cyclization is accomplished by reacting the disulfide-amide with a halogenating agent. Any halogenating agent may be employed in this reaction. Typical halogenating agents include chlorine, bromine, sulfuryl chloride, sulfuryl bromide, N-chlorosuccinimide, N-bromosuccinimide, iodine monochloride, etc. Bromine and chlorine are preferred halogenating agents. Cyclization of the disulfide-amide will take place when 3 mole equivalents of halogenating agent are employed in the reaction. The cyclization reaction is typically carried out at a temperature in the range 0 to 100°C in an inert, non-aqueous solvent, such as benzene, toluene, xylene, ethyl acetate, or ethylene dichloride. When R is methyl in the disulfide-amide reactant of formula (II), 2-methyl-4-isothiazolin-3-one is

obtained. By providing an excess of halogenating agent, the isothiazolone can be halogenated at the 5-position, giving 5-chloro-2-methyl-4-isothiazolin-3-one, when the halogenating agent is chlorine.

The 3-isothiazolones present in the Kathon^(R) formulations are aqueous mixtures of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one. These compounds are present in ratios, by weight, between 2:1 and 4:1 as the active ingredients in the formulations. The formulations additionally contain magnesium salts, such as magnesium nitrate and magnesium chloride, as stabilizers, and water.

Synergism between two antimicrobials is exhibited when the observed activity of the combination is greater than the expected additive activity of the two separate antimicrobials. We have discovered that the combination of our Suttocide^(R) A formulation which is an aqueous solution of sodium hydroxymethylaminoacetate with a Kathon^(R) formulation exhibits synergism in both microbial inhibition and microbiocidal activity. The synergistic activity appears in Suttocide^(R) to Kathon^(R) ratios, by weight, from less than 2:1 to approximately 60:1. Because the Kathon^(R) formulations are highly diluted with water and magnesium salts, the actual ratio of active ingredients in the combination of Suttocide^(R) A and Kathon^(R) will be much higher, on the order of approximately 100:1 to 4000:1.

The examples which follow report our experiments carried out with a Kathon^(R) formulation identified as Kathon^(R) CG (cosmetic grade), a popular formulation used as a preservative in cosmetics and toiletries, and Suttocide^(R) A. The composition of Kathon^(R) CG is:

Active ingredients	
5-chloro-2-methyl-4-isothiazolin-3-one	1.15%
2-methyl-4-isothiazolin-3-one	0.35%
Inert Ingredients	
Magnesium salts	23.0%
Water	75.5%
	100.0%

Suttocide^(R) A is sodium hydroxymethylaminoacetate (100% active ingredient).

The results reported are considered to be applicable to all Kathon^(R) formulations, since the active ingredients are the same, as well as formulations based upon other isothiazolones of formula (I) in combination with

Suttocide A or other hydroxymethylaminoacetic acid derivatives previously described.

EXAMPLE I

A minimum inhibitory concentration was determined for each component and their combination versus the following challenge inocula:

<i>Pseudomonas aeruginosa</i>	ATCC # 9027
<i>Candida albicans</i>	ATCC # 10231
<i>Aspergillus niger</i>	ATCC # 16404

Each sample series was diluted 1:1 using 5 mls. of Trypticase Soy Broth and 5 mls. of product. The same procedure was used to prepare the yeast and mold challenge samples except the dilution broth used was Sabouraud Dextrose Broth. All diluted samples were then inoculated using 0.1 cc of each challenge inocula. All tubes were incubated at 37°C for 24 to 48 hours and then examined for turbidity. The "MIC" for each product is the last clear tube before the first tube showing turbidity.

Table I lists minimum inhibitory concentrations (MIC) of Suttocide^(R) A (100% basis) and Kathon^(R) CG (1.5% solution) for a gramnegative bacterium, *Pseudomonas aeruginosa* (ATCC No. 9027), a yeast *Candida albicans* (ATCC No. 10231), and a mold, *Aspergillus niger* (ATCC No. 16404). MICs are the minimum concentrations at which each antimicrobial or combination prevents growth of microorganisms. A combination of half the amount of Suttocide^(R) A plus half the amount of Kathon^(R) CG would be expected to be the minimum required level needed to inhibit growth if the activities are additive. If combination quantities containing less than half of each are inhibiting, it demonstrates greater than expected activity, and therefore synergism between the two antimicrobials.

Table I Minimum Inhibitory Concentrations (all concentrations in ppm)

	<i>P. aeruginosa</i> (ATCC 9027)	<i>C. albicans</i> (ATCC 10231)	<i>A. niger</i> (ATCC 16404)
Suttocide ^(R) A (100% active ingredient)	313	1250	313
Kathon ^(R) CG (1.5% active ingredient)	> 333	42	21
Expected MIC (half concentrations)	157/>167	625/21	157/11
Suttocide ^(R) A/ Kathon ^(R) CG			
Observed MIC	157/83	157/21	157/0.67
Suttocide ^(R) A/ Kathon ^(R) CG			or 79/1.33

The data recorded in Table I demonstrates that for combinations of the two antimicrobials, the observed MICs for the combinations of Suttocide^(R) A and Kathon^(R) CG was less than the expected MIC's based upon the results for each antimicrobial individually tested reduced to half concentrations. These results for the combination of Suttocide^(R) A and Kathon^(R) clearly demonstrate synergism in the combination.

EXAMPLE 2

A minimum concentration for a killing (biocidal) effect was determined for each component and their combination on *E. coli* (ATCC # 8739), a coliform bacterium.

The bacteria were cultivated, plated and maintained in Trypticase Soy Broth (TSB) and/or Trypticase Soy Agar (TSA). All bacterial dilutions were done using TSB.

For each compound a set-up entailed a total of 10-12 test tubes with each tube containing 2.5 ml of the appropriate concentration of the compound and 2.5 ml of the appropriate test organism. The concentration of the organism was adjusted to about 10^6 /ml and this was confirmed by standard plate counts.

All test tubes containing compound plus E. coli were then incubated at 37°C for 24, 48, and 72 hrs. After each period of incubation 0.01 ml (10 μ l) from each tube was dispensed into appropriate sterile agar plates. The plates were then incubated at 37°C for 24-48 hours and the resulting colonies counted.

The counts were compared with the original counts. This comparison permitted the determination of 97-100% kill for each compound at each concentration tested. Less than 97% kill was reported as growth. The lowest concentration of compound or combination of compounds for which 97-100% kill occurred was the minimum biocidal concentration (MBC).

The results of this test are recorded in Table II.

Table II Minimum Biocidal Concentrations (all concentrations in ppm)

E. coli
(ATCC 8739)

Suttocide ^(R) A (100% active ingredient)	625
Kathon ^(R) CG (1.5% active ingredients)	160
Expected MBC(half concentrations)	313/80
Suttocide ^(R) A/Kathon ^(R) CG	
Observed MBC Suttocide ^(R) A/Kathon ^(R) CG	313/53

The results show that the MBC for the combination of Suttocide^(R) A and Kathon^(R) was less than half of each antimicrobial individually tested reduced to half concentrations.

The synergistic microbial inhibiting and biocidal activity of the combination of hydroxymethylaminoacetic acid, its salts and lower alkyl esters and the 3-isothiazolones, has significant practical applications since it allows lesser amounts of the 3-isothiazolone components to be used to achieve an equivalent microbial inhibiting or biocidal effect. This is important since the 3-isothiazolones are notoriously corrosive and highly irritating to skin. Hence, the composition of the present invention can be used in all applications where the 3-isothiazolones, particularly the Kathon^(R) family of products have been proposed, with less toxicities.

Such applications include, but are not limited to, use as an anti-

microbial preservative in cosmetics, toiletries and household cleaning properties, use as a biocide for synthetic latexes, emulsion paints and other coatings, adhesives, polishes, carpet backing compositions, surfactants, metalworking fluids, industrial and domestic water treatment including cooling tower systems and swimming pools, adhesive mats, drilling mud formulations, painting pastes, spin finish emulsions, polymer dispersions, fuels and in other substances susceptible to contamination by microorganisms. A further important application is as a slimicide for slime control in the manufacture of paper from wood pulp.

The amount of the composition of the invention incorporated into a product will, of course, depend upon the particular product being treated as well as the purpose of the treatment, i.e., preservative or biocide. Generally, amounts to no greater than 1.0%, by weight based upon the weight of the product, of active ingredients will be effective for most uses. However, it is understood that due to the diversity in applications in which the composition may be used, this weight percentage is not an absolute maximum.

The composition of the invention may be incorporated into a product requiring antimicrobial protection by pre-mixing the individual components, e.g., Suttocide^(R) A and Kathon^(R), in a common carrier and then incorporating the pre-mixed composition into the product or by incorporating the individual components into the product separately. The invention, therefore, contemplates both pre-mixed compositions containing the antimicrobial components as well as compositions which are prepared only as part of the formulation of a product requiring antimicrobial protection. In either case, the preferred compounds and weight ratios of these compounds to one another are the same. In particular, the combination of sodium hydromethylaminoacetate with 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in which the weight ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one is between about 2:1 and 4:1 is most preferred. This composition is obtained by formulating the product to be preserved with effective amounts of Suttocide^(R) A (sodium hydroxymethylaminoacetate) and any one of the numerous Kathon^(R) formulations.

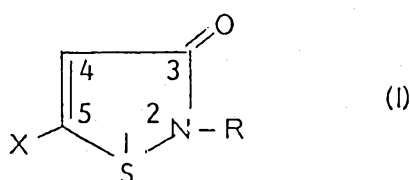
While the invention has now been described in terms of certain preferred embodiments, and exemplified with respect thereto, one skilled in

the art will readily appreciate that various modifications, changes, omissions and substitutions may be made without departing from the spirit thereof. It is intended, therefore, that the present invention be limited solely by the scope of the following claims.

1. A method of
2. for the purpose
3. of the present
4. invention, the
5. following steps
6. are performed:
7. a. the first
8. step is to
9. determine the
10. value of the
11. first term of
12. the series
13. b. the second
14. step is to
15. determine the
16. value of the
17. second term of
18. the series
19. c. the third
20. step is to
21. determine the
22. value of the
23. third term of
24. the series
25. d. the fourth
26. step is to
27. determine the
28. value of the
29. fourth term of
30. the series
31. e. the fifth
32. step is to
33. determine the
34. value of the
35. fifth term of
36. the series
37. f. the sixth
38. step is to
39. determine the
40. value of the
41. sixth term of
42. the series
43. g. the seventh
44. step is to
45. determine the
46. value of the
47. seventh term of
48. the series
49. h. the eighth
50. step is to
51. determine the
52. value of the
53. eighth term of
54. the series
55. i. the ninth
56. step is to
57. determine the
58. value of the
59. ninth term of
60. the series
61. j. the tenth
62. step is to
63. determine the
64. value of the
65. tenth term of
66. the series
67. k. the eleventh
68. step is to
69. determine the
70. value of the
71. eleventh term of
72. the series
73. l. the twelfth
74. step is to
75. determine the
76. value of the
77. twelfth term of
78. the series
79. m. the thirteenth
80. step is to
81. determine the
82. value of the
83. thirteenth term of
84. the series
85. n. the fourteenth
86. step is to
87. determine the
88. value of the
89. fourteenth term of
90. the series
91. o. the fifteenth
92. step is to
93. determine the
94. value of the
95. fifteenth term of
96. the series
97. p. the sixteenth
98. step is to
99. determine the
100. value of the
101. sixteenth term of
102. the series
103. q. the seventeenth
104. step is to
105. determine the
106. value of the
107. seventeenth term of
108. the series
109. r. the eighteenth
110. step is to
111. determine the
112. value of the
113. eighteenth term of
114. the series
115. s. the nineteenth
116. step is to
117. determine the
118. value of the
119. nineteenth term of
120. the series
121. t. the twentieth
122. step is to
123. determine the
124. value of the
125. twentieth term of
126. the series
127. u. the twenty-first
128. step is to
129. determine the
130. value of the
131. twenty-first term of
132. the series
133. v. the twenty-second
134. step is to
135. determine the
136. value of the
137. twenty-second term of
138. the series
139. w. the twenty-third
140. step is to
141. determine the
142. value of the
143. twenty-third term of
144. the series
145. x. the twenty-fourth
146. step is to
147. determine the
148. value of the
149. twenty-fourth term of
150. the series
151. y. the twenty-fifth
152. step is to
153. determine the
154. value of the
155. twenty-fifth term of
156. the series
157. z. the twenty-sixth
158. step is to
159. determine the
160. value of the
161. twenty-sixth term of
162. the series
163. aa. the twenty-seventh
164. step is to
165. determine the
166. value of the
167. twenty-seventh term of
168. the series
169. ab. the twenty-eighth
170. step is to
171. determine the
172. value of the
173. twenty-eighth term of
174. the series
175. ac. the twenty-ninth
176. step is to
177. determine the
178. value of the
179. twenty-ninth term of
180. the series
181. ad. the thirtieth
182. step is to
183. determine the
184. value of the
185. thirtieth term of
186. the series
187. ae. the thirty-first
188. step is to
189. determine the
190. value of the
191. thirty-first term of
192. the series
193. af. the thirty-second
194. step is to
195. determine the
196. value of the
197. thirty-second term of
198. the series
199. ag. the thirty-third
200. step is to
201. determine the
202. value of the
203. thirty-third term of
204. the series
205. ah. the thirty-fourth
206. step is to
207. determine the
208. value of the
209. thirty-fourth term of
210. the series
211. ai. the thirty-fifth
212. step is to
213. determine the
214. value of the
215. thirty-fifth term of
216. the series
217. aj. the thirty-sixth
218. step is to
219. determine the
220. value of the
221. thirty-sixth term of
222. the series
223. ak. the thirty-seventh
224. step is to
225. determine the
226. value of the
227. thirty-seventh term of
228. the series
229. al. the thirty-eighth
230. step is to
231. determine the
232. value of the
233. thirty-eighth term of
234. the series
235. am. the thirty-ninth
236. step is to
237. determine the
238. value of the
239. thirty-ninth term of
240. the series
241. an. the fortieth
242. step is to
243. determine the
244. value of the
245. fortieth term of
246. the series
247. ao. the forty-first
248. step is to
249. determine the
250. value of the
251. forty-first term of
252. the series
253. ap. the forty-second
254. step is to
255. determine the
256. value of the
257. forty-second term of
258. the series
259. aq. the forty-third
260. step is to
261. determine the
262. value of the
263. forty-third term of
264. the series
265. ar. the forty-fourth
266. step is to
267. determine the
268. value of the
269. forty-fourth term of
270. the series
271. as. the forty-fifth
272. step is to
273. determine the
274. value of the
275. forty-fifth term of
276. the series
277. at. the forty-sixth
278. step is to
279. determine the
280. value of the
281. forty-sixth term of
282. the series
283. au. the forty-seventh
284. step is to
285. determine the
286. value of the
287. forty-seventh term of
288. the series
289. av. the forty-eighth
290. step is to
291. determine the
292. value of the
293. forty-eighth term of
294. the series
295. aw. the forty-ninth
296. step is to
297. determine the
298. value of the
299. forty-ninth term of
300. the series
301. ax. the fiftieth
302. step is to
303. determine the
304. value of the
305. fiftieth term of
306. the series
307. ay. the fifty-first
308. step is to
309. determine the
310. value of the
311. fifty-first term of
312. the series
313. az. the fifty-second
314. step is to
315. determine the
316. value of the
317. fifty-second term of
318. the series
319. ba. the fifty-third
320. step is to
321. determine the
322. value of the
323. fifty-third term of
324. the series
325. bb. the fifty-fourth
326. step is to
327. determine the
328. value of the
329. fifty-fourth term of
330. the series
331. bc. the fifty-fifth
332. step is to
333. determine the
334. value of the
335. fifty-fifth term of
336. the series
337. bd. the fifty-sixth
338. step is to
339. determine the
340. value of the
341. fifty-sixth term of
342. the series
343. be. the fifty-seventh
344. step is to
345. determine the
346. value of the
347. fifty-seventh term of
348. the series
349. bf. the fifty-eighth
350. step is to
351. determine the
352. value of the
353. fifty-eighth term of
354. the series
355. bg. the fifty-ninth
356. step is to
357. determine the
358. value of the
359. fifty-ninth term of
360. the series
361. bh. the sixtieth
362. step is to
363. determine the
364. value of the
365. sixtieth term of
366. the series
367. bi. the sixty-first
368. step is to
369. determine the
370. value of the
371. sixty-first term of
372. the series
373. bj. the sixty-second
374. step is to
375. determine the
376. value of the
377. sixty-second term of
378. the series
379. bk. the sixty-third
380. step is to
381. determine the
382. value of the
383. sixty-third term of
384. the series
385. bl. the sixty-fourth
386. step is to
387. determine the
388. value of the
389. sixty-fourth term of
390. the series
391. bm. the sixty-fifth
392. step is to
393. determine the
394. value of the
395. sixty-fifth term of
396. the series
397. bn. the sixty-sixth
398. step is to
399. determine the
400. value of the
401. sixty-sixth term of
402. the series
403. bo. the sixty-seventh
404. step is to
405. determine the
406. value of the
407. sixty-seventh term of
408. the series
409. bp. the sixty-eighth
410. step is to
411. determine the
412. value of the
413. sixty-eighth term of
414. the series
415. bq. the sixty-ninth
416. step is to
417. determine the
418. value of the
419. sixty-ninth term of
420. the series
421. br. the seventieth
422. step is to
423. determine the
424. value of the
425. seventieth term of
426. the series
427. bs. the seventy-first
428. step is to
429. determine the
430. value of the
431. seventy-first term of
432. the series
433. bt. the seventy-second
434. step is to
435. determine the
436. value of the
437. seventy-second term of
438. the series
439. bu. the seventy-third
440. step is to
441. determine the
442. value of the
443. seventy-third term of
444. the series
445. bv. the seventy-fourth
446. step is to
447. determine the
448. value of the
449. seventy-fourth term of
450. the series
451. bw. the seventy-fifth
452. step is to
453. determine the
454. value of the
455. seventy-fifth term of
456. the series
457. bx. the seventy-sixth
458. step is to
459. determine the
460. value of the
461. seventy-sixth term of
462. the series
463. by. the seventy-seventh
464. step is to
465. determine the
466. value of the
467. seventy-seventh term of
468. the series
469. bz. the seventy-eighth
470. step is to
471. determine the
472. value of the
473. seventy-eighth term of
474. the series
475. ca. the seventy-ninth
476. step is to
477. determine the
478. value of the
479. seventy-ninth term of
480. the series
481. cb. the eightieth
482. step is to
483. determine the
484. value of the
485. eightieth term of
486. the series
487. cc. the eighty-first
488. step is to
489. determine the
490. value of the
491. eighty-first term of
492. the series
493. cd. the eighty-second
494. step is to
495. determine the
496. value of the
497. eighty-second term of
498. the series
499. ce. the eighty-third
500. step is to
501. determine the
502. value of the
503. eighty-third term of
504. the series
505. cd. the eighty-fourth
506. step is to
507. determine the
508. value of the
509. eighty-fourth term of
510. the series
511. ce. the eighty-fifth
512. step is to
513. determine the
514. value of the
515. eighty-fifth term of
516. the series
517. cf. the eighty-sixth
518. step is to
519. determine the
520. value of the
521. eighty-sixth term of
522. the series
523. cg. the eighty-seventh
524. step is to
525. determine the
526. value of the
527. eighty-seventh term of
528. the series
529. ch. the eighty-eighth
530. step is to
531. determine the
532. value of the
533. eighty-eighth term of
534. the series
535. ci. the eighty-ninth
536. step is to
537. determine the
538. value of the
539. eighty-ninth term of
540. the series
541. cj. the ninetieth
542. step is to
543. determine the
544. value of the
545. ninetieth term of
546. the series
547. ck. the ninety-first
548. step is to
549. determine the
550. value of the
551. ninety-first term of
552. the series
553. cl. the ninety-second
554. step is to
555. determine the
556. value of the
557. ninety-second term of
558. the series
559. cm. the ninety-third
560. step is to
561. determine the
562. value of the
563. ninety-third term of
564. the series
565. cn. the ninety-fourth
566. step is to
567. determine the
568. value of the
569. ninety-fourth term of
570. the series
571. co. the ninety-fifth
572. step is to
573. determine the
574. value of the
575. ninety-fifth term of
576. the series
577. cp. the ninety-sixth
578. step is to
579. determine the
580. value of the
581. ninety-sixth term of
582. the series
583. cq. the ninety-seventh
584. step is to
585. determine the
586. value of the
587. ninety-seventh term of
588. the series
589. cr. the ninety-eighth
590. step is to
591. determine the
592. value of the
593. ninety-eighth term of
594. the series
595. cs. the ninety-ninth
596. step is to
597. determine the
598. value of the
599. ninety-ninth term of
600. the series
601. ct. the one hundredth
602. step is to
603. determine the
604. value of the
605. one hundredth term of
606. the series
607. cu. the one hundred-first
608. step is to
609. determine the
610. value of the
611. one hundred-first term of
612. the series
613. cv. the one hundred-second
614. step is to
615. determine the
616. value of the
617. one hundred-second term of
618. the series
619. cw. the one hundred-third
620. step is to
621. determine the
622. value of the
623. one hundred-third term of
624. the series
625. cx. the one hundred-fourth
626. step is to
627. determine the
628. value of the
629. one hundred-fourth term of
630. the series
631. cy. the one hundred-fifth
632. step is to
633. determine the
634. value of the
635. one hundred-fifth term of
636. the series
637. cz. the one hundred-sixth
638. step is to
639. determine the
640. value of the
641. one hundred-sixth term of
642. the series
643. da. the one hundred-seventh
644. step is to
645. determine the
646. value of the
647. one hundred-seventh term of
648. the series
649. db. the one hundred-eighth
650. step is to
651. determine the
652. value of the
653. one hundred-eighth term of
654. the series
655. dc. the one hundred-ninth
656. step is to
657. determine the
658. value of the
659. one hundred-ninth term of
660. the series
661. dd. the one hundred-tenth
662. step is to
663. determine the
664. value of the
665. one hundred-tenth term of
666. the series
667. de. the one hundred-eleventh
668. step is to
669. determine the
670. value of the
671. one hundred-eleventh term of
672. the series
673. de. the one hundred-twelfth
674. step is to
675. determine the
676. value of the
677. one hundred-twelfth term of
678. the series
679. df. the one hundred-thirteenth
680. step is to
681. determine the
682. value of the
683. one hundred-thirteenth term of
684. the series
685. dg. the one hundred-fourteenth
686. step is to
687. determine the
688. value of the
689. one hundred-fourteenth term of
690. the series
691. dh. the one hundred-fifteenth
692. step is to
693. determine the
694. value of the
695. one hundred-fifteenth term of
696. the series
697. di. the one hundred-sixteenth
698. step is to
699. determine the
700. value of the
701. one hundred-sixteenth term of
702. the series
703. dj. the one hundred-seventeenth
704. step is to
705. determine the
706. value of the
707. one hundred-seventeenth term of
708. the series
709. dk. the one hundred-eighteenth
710. step is to
711. determine the
712. value of the
713. one hundred-eighteenth term of
714. the series
715. dl. the one hundred-nineteenth
716. step is to
717. determine the
718. value of the
719. one hundred-nineteenth term of
720. the series
721. dm. the one hundred-twentieth
722. step is to
723. determine the
724. value of the
725. one hundred-twentieth term of
726. the series
727. dn. the one hundred-twenty-first
728. step is to
729. determine the
730. value of the
731. one hundred-twenty-first term of
732. the series
733. do. the one hundred-twenty-second
734. step is to
735. determine the
736. value of the
737. one hundred-twenty-second term of
738. the series
739. dp. the one hundred-twenty-third
740. step is to
741. determine the
742. value of the
743. one hundred-twenty-third term of
744. the series
745. dq. the one hundred-twenty-fourth
746. step is to
747. determine the
748. value of the
749. one hundred-twenty-fourth term of
750. the series
751. dr. the one hundred-twenty-fifth
752. step is to
753. determine the
754. value of the
755. one hundred-twenty-fifth term of
756. the series
757. ds. the one hundred-twenty-sixth
758. step is to
759. determine the
760. value of the
761. one hundred-twenty-sixth term of
762. the series
763. dt. the one hundred-twenty-seventh
764. step is to
765. determine the
766. value of the
767. one hundred-twenty-seventh term of
768. the series
769. du. the one hundred-twenty-eighth
770. step is to
771. determine the
772. value of the
773. one hundred-twenty-eighth term of
774. the series
775. dv. the one hundred-twenty-ninth
776. step is to
777. determine the
778. value of the
779. one hundred-twenty-ninth term of
780. the series
781. dw. the one hundred-thirtieth
782. step is to
783. determine the
784. value of the
785. one hundred-thirtieth term of
786. the series
787. dx. the one hundred-thirty-first
788. step is to
789. determine the
790. value of the
791. one hundred-thirty-first term of
792. the series
793. dy. the one hundred-thirty-second
794. step is to
795. determine the
796. value of the
797. one hundred-thirty-second term of
798. the series
799. dz. the one hundred-thirty-third
800. step is to
801. determine the
802. value of the
803. one hundred-thirty-third term of
804. the series
805. ea. the one hundred-thirty-fourth
806. step is to
807. determine the
808. value of the
809. one hundred-thirty-fourth term of
810. the series
811. eb. the one hundred-thirty-fifth
812. step is to
813. determine the
814. value of the
815. one hundred-thirty-fifth term of
816. the series
817. ec. the one hundred-thirty-sixth
818. step is to
819. determine the
820. value of the
821. one hundred-thirty-sixth term of
822. the series
823. ed. the one hundred-thirty-seventh
824. step is to
825. determine the
826. value of the
827. one hundred-thirty-seventh term of
828. the series
829. ee. the one hundred-thirty-eighth
830. step is to
831. determine the
832. value of the
833. one hundred-thirty-eighth term of
834. the series
835. ef. the one hundred-thirty-ninth
836. step is to
837. determine the
838. value of the
839. one hundred-thirty-ninth term of
840. the series
841. eg. the one hundred-fortieth
842. step is to
843. determine the
844. value of the
845. one hundred-fortieth term of
846. the series
847. eh. the one hundred-forty-first
848. step is to
849. determine the
850. value of the
851. one hundred-forty-first term of
852. the series
853. ei. the one hundred-forty-second
854. step is to
855. determine the
856. value of the
857. one hundred-forty-second term of
858. the series
859. ej. the one hundred-forty-third
860. step is to
861. determine the
862. value of the
863. one hundred-forty-third term of
864. the series
865. ek. the one hundred-forty-fourth
866. step is to
867. determine the
868. value of the
869. one hundred-forty-fourth term of
870. the series
871. el. the one hundred-forty-fifth
872. step is to
873. determine the
874. value of the
875. one hundred-forty-fifth term of
876. the series
877. em. the one hundred-forty-sixth
878. step is to
879. determine the
880. value of the
881. one hundred-forty-sixth term of
882. the series
883. en. the one hundred-forty-seventh
884. step is to
885. determine the
886. value of the
887. one hundred-forty-seventh term of
888. the series
889. eo. the one hundred-forty-eighth
890. step is to
891. determine the
892. value of the
893. one hundred-forty-eighth term of
894. the series
895. ep. the one hundred-forty-ninth
896. step is to
897. determine the
898. value of the
899. one hundred-forty-ninth term of
900. the series
901. eq. the one hundred-fiftieth
902. step is to
903. determine the
904. value of the
905. one hundred-fiftieth term of
906. the series
907. er. the one hundred-fifty-first
908. step is to
909. determine the
910. value of the
911. one hundred-fifty-first term of
912. the series
913. es. the one hundred-fifty-second
914. step is to
915. determine the
916. value of the
917. one hundred-fifty-second term of
918. the series
919. et. the one hundred-fifty-third
920. step is to
921. determine the
922. value of the
923. one hundred-fifty-third term of
924. the series
925. eu. the one hundred-fifty-fourth
926. step is to
927. determine the
928. value of the
929. one hundred-fifty-fourth term of
930. the series
931. ev. the one hundred-fifty-fifth
932. step is to
933. determine the
934. value of the
935. one hundred-fifty-fifth term of
936. the series
937. ew. the one hundred-fifty-sixth
938. step is to
939. determine the
940. value of the
941. one hundred-fifty-sixth term of
942. the series
943. ex. the one hundred-fifty-seventh
944. step is to
945. determine the
946. value of the
947. one hundred-fifty-seventh term of
948. the series
949. ey. the one hundred-fifty-eighth
950. step is to
951. determine the
952. value of the
953. one hundred-fifty-eighth term of
954. the series
955. ez. the one hundred-fifty-ninth
956. step is to
957. determine the
958. value of the
959. one hundred-fifty-ninth term of
960. the series
961. fa. the one hundred-sixtieth
962. step is to
963. determine the
964. value of the
965. one hundred-sixtieth term of
966. the series
967. fb. the one hundred-sixty-first
968. step is to
969. determine the
970. value of the
971. one hundred-sixty-first term of
972. the series
973. fc. the one hundred-sixty-second
974. step is to
975. determine the
976. value of the
977. one hundred-sixty-second term of
978. the series
979. fd. the one hundred-sixty-third
980. step is to
981. determine the
982. value of the
983. one hundred-sixty-third term of
984. the series
985. fe. the one hundred-sixty-fourth
986. step is to
987. determine the
988. value of the
989. one hundred-sixty-fourth term of
990. the series
991. ff. the one hundred-sixty-fifth
992. step is to
993. determine the
994. value of the
995. one hundred-sixty-fifth term of
996. the series
997. fg. the one hundred-sixty-sixth
998. step is to
999. determine the
1000. value of the
1001. one hundred-sixty-sixth term of
1002. the series
1003. fh. the one hundred-sixty-seventh
1004. step is to
1005. determine the
1006. value of the
1007. one hundred-sixty-seventh term of
1008. the series
1009. fi. the one hundred-sixty-eighth
1010. step is to
1011. determine the
1012. value of the
1013. one hundred-sixty-eighth term of
1014. the series
1015. fj. the one hundred-sixty-ninth
1016. step is to
1017. determine the
1018. value of the
1019. one hundred-sixty-ninth term of
1020. the series
1021. fk. the one hundred-seventieth
1022. step is to
1023. determine the
1024. value of the
1025. one hundred-seventieth term of
1026. the series
1027. fl. the one hundred-seventy-first
1028. step is to
1029. determine the
1030. value of the
1031. one hundred-seventy-first term of
1032. the series
1033. fm. the one hundred-seventy-second
1034. step is to
1035. determine the
1036. value of the
1037. one hundred-seventy-second term of
1038. the series
1039. fn. the one hundred-seventy-third
1040. step is to
1041. determine the
1042. value of the
1043. one hundred-seventy-third term of
1044. the series
1045. fo. the one hundred-seventy-fourth
1046. step is to
1047. determine the
1048. value of the
1049. one hundred-seventy-fourth term of
1050. the series
1051. fp. the one hundred-seventy-fifth
1052. step is to
1053. determine the
1054. value of the
1055. one hundred-seventy-fifth term of
1056. the series
1057. fq. the one hundred-seventy-sixth
1058. step is to
1059. determine the
1060. value of the
1061. one hundred-seventy-sixth term of
1062. the series
1063. fr. the one hundred-seventy-seventh
1064. step is to
1065. determine the
1066. value of the
1067. one hundred-seventy-seventh term of
1068. the series
1069. fs. the one hundred-seventy-eighth
1070. step is to
1071. determine the
1072. value of the
1073. one hundred-seventy-eighth term of
1074. the series
1075. ft. the one hundred-seventy-ninth
1076. step is to
1077. determine the
1078. value of the
1079. one hundred-seventy-ninth term of
1080. the series
1081. fu. the one hundred-eightieth
1082. step is to
1083. determine the
1084. value of the
1085. one hundred-eightieth term of
1086. the series
1087. fv. the one hundred-eighty-first
1088. step is to
1089. determine the
1090. value of the
1091. one hundred-eighty-first term of
1092. the series
1093. fw. the one hundred-eighty-second
1094. step is to
1095. determine the
1096. value of the
1097. one hundred-eighty-second term of
1098. the series
1099. fx. the one hundred-eighty-third
1100. step is to
1101. determine the
1102. value of the
1103. one hundred-eighty-third term of
1104. the series
1105. fy. the one hundred-eighty-fourth
1106. step is to
1107. determine the
1108. value of the
1109. one hundred-eighty-fourth term of
1110. the series
1111. fz. the one hundred-eighty-fifth
1112. step is to
1113. determine the
1114. value of the
1115. one hundred-eighty-fifth term of
1116. the series
1117. ga. the one hundred-eighty-sixth
1118. step is to
1119. determine the
1120. value of the
1121. one hundred-eighty-sixth term of
1122. the series
1123. gb. the one hundred-eighty-seventh
1124. step is to
1125. determine the
1126. value of the
1127. one hundred-eighty-seventh term of
1128. the series
1129. gc. the one hundred-eighty-eighth
1130. step is to
1131. determine the
1132. value of the
1133. one hundred-eighty-eighth term of
1134. the series
1135. gd. the one hundred-eighty-ninth
1136. step is to
1137. determine the
1138. value of the
1139. one hundred-eighty-ninth term of
1140. the series
1141. ge. the one hundred-ninetieth
1142. step is to
1143. determine the
1144. value of the
1145. one hundred-ninetieth term of
1146. the series
1147. gf. the one hundred-ninety-first
1148. step is to
1149. determine the
1150. value of the
1151. one hundred-ninety-first term of
1152. the series
1153. gh. the one hundred-ninety-second
1154. step is to
1155. determine the
1156. value of the
1157. one hundred-ninety-second term of
1158. the series
1159. gg. the one hundred-ninety-third
1160. step is to
1161. determine the
1162. value of the
1163. one hundred-ninety-third term of
1164. the series
1165. gh. the one hundred-ninety-fourth
1166. step is to
1167. determine the
1168. value of the
1169. one hundred-ninety-fourth term of
1170. the series
1171. gi. the one hundred-ninety-fifth
1172. step is to
1173. determine the
1174. value of the
1175. one hundred-ninety-fifth term of
1176. the series
1177. hg. the one hundred-ninety-sixth
1178. step is to
1179. determine the
1180. value of the
1181. one hundred-ninety-sixth term of
1182. the series
1183. ih. the one hundred-ninety-seventh
1184. step is to
1185. determine the
1186. value of the
1187. one hundred-ninety-seventh term of
1188. the series
1189. ii. the one hundred-ninety-eighth
1190. step is to
1191. determine the
1192. value of the
1193. one hundred-ninety-eighth term of
1194. the series
1195. ij. the one hundred-ninety-ninth
1196. step is to
1197. determine the
1198. value of the
1199. one hundred-ninety-ninth term of
1200. the series
1201. ik. the one hundred-twentieth
1202. step is to
1203. determine the
1204. value of the
1205. one hundred-twentieth term of
1206. the series
1207. il. the one hundred-twenty-first
1208. step is to
1209. determine the
1210. value of the
1211. one hundred-twenty-first term of
1212. the series
1213. im. the one hundred-twenty-second
1214. step is to
1215. determine the
1216. value of the
1217. one hundred-twenty-second term of
1218. the series
1219. in. the one hundred-twenty-third
1220. step is to
1221. determine the
1222. value of the
1223. one hundred-twenty-third term of
1224. the series
1225. io. the one hundred-twenty-fourth
1226. step is to
1227. determine the
1228. value of the
1229. one hundred-twenty-fourth term of
1230. the series
1231. ip. the one hundred

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A ~~composition of matter~~ ^{biocidal and antimicrobial composition} comprising (i) a compound selected from the group consisting of hydroxymethylaminoacetic acid, its salts and its lower alkyl esters and (ii) one or more compounds of the formula (I):



wherein R is a lower alkyl group and X is hydrogen or a halogen.

2. The composition of claim 1, wherein said compound (i) is a member selected from the group consisting of sodium hydroxymethylaminoacetate, potassium hydroxymethylaminoacetate, aluminum hydroxymethylaminoacetate, calcium hydroxymethylaminoacetate, magnesium hydroxymethylaminoacetate, copper hydroxymethylaminoacetate, zinc hydroxymethylaminoacetate, methyl hydroxymethylaminoacetate and hydroxymethylaminoacetic acid.

3. The composition of claim 2 wherein said compound (i) is sodium hydroxymethylaminoacetate.

4. The composition of claim 3, wherein said one or more compounds of formula (I) are members selected from the group consisting of 5-chloro-2-methyl-4-isothiazolin-3-one, 2-methyl-4-isothiazolin-3-one and mixtures thereof.

5. The composition of claim 4, wherein said compositions contain 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, present in a ratio, by weight, between ~~about~~ 2:1 and 4:1.



6. The composition of claim 5, wherein the ratio, by weight, of sodium hydroxymethylaminoacetate to the sum of the weights of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one is greater than ~~about~~ 100:1 and less than ~~about~~ 4000:1.

7. The composition of claim 6, further comprising magnesium salts and water.

8. A method for inhibiting microbial growth in a substance requiring microbial inhibition comprising incorporating into the substance an effective microbial growth inhibiting amount of composition of any one of claims 1, 2, 3, 4, 5, 6 or 7.

9. A preserved product comprising an effective microbial growth inhibiting amount of the composition of any one of claims 1, 2, 3, 4, 5, 6 or 7.

10. A method for killing microorganisms comprising contacting said microorganisms with an effective biocidal amount of the composition of any one of claims 1, 2, 3, 4, 5, 6, or 7.

~~11. Biocidal compositions or methods, substantially as hereinbefore described with reference to the Examples.~~

~~12. The steps, features, compositions and compounds referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two or more of said steps or features.~~

~~Dated this 4th day of March 1987~~

SUTTON LABORATORIES, INC.

By its Patent Attorneys

~~DAVIES AND COLLISON~~



1 11. Biocidal and antimicrobial compositions in
2 accordance with claim 1 or methods of use of same
3 substantially as hereinbefore described with reference to
4 the Examples.

5

6

7

8 DATED THIS 18th December, 1989

9 DAVIES & COLLISON

10 Fellows Institute of Patent

11 Attorneys of Australia.

12 Patent Attorneys for the Applicant

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

