(12) STANDARD PATENT (11) Application No. **AU 2005200909 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Antimicrobial composition containing N-(n-butyl)-1,2-benzisothiazolin-3-one

(51) International Patent Classification(s)
A01N 43/80 (2006.01)

(21) Application No: **2005200909** (22) Date of Filing: **2005.02.28**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60550503	**2004.03.05**	**US**

(43) Publication Date: **2005.09.22**
(43) Publication Journal Date: **2005.09.22**
(44) Accepted Journal Date: **2010.09.30**

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(56) Related Art
JP 01-224306 A
EP 1283096 A1
JP 2001-302418 A
EP 0608911 B2
AU 2001272419 B2
US 2003/0168626 A1

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ABSTRACT OF THE DISCLOSURE

An antimicrobial composition comprising: (a) N-(n-butyl)-1,2-benzisothiazolin-3-one; and (b) 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one.

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AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

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INVENTION TITLE:

Antimicrobial composition containing N-(n-butyl)-1,2-benzisothiazolin-3-one

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

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This invention relates to combinations of N-(n-butyl)-1,2-benzisothiazolin-3-one with selected antimicrobial compounds, the combinations having greater activity than would be observed for the individual antimicrobial compounds.

Use of combinations of at least two antimicrobial compounds can broaden potential markets, reduce use concentrations and costs, and reduce waste. In some cases, commercial antimicrobial compounds cannot provide effective control of microorganisms, even at high use concentrations, due to weak activity against certain types of microorganisms, e.g., those resistant to some antimicrobial compounds. Combinations of different antimicrobial compounds are sometimes used to provide overall control of microorganisms in a particular end use environment. For example, WO 02/17716 discloses a synergistic combination of N-(n-butyl)-1,2-benzisothiazolin-3-one (n-BBIT) and 2-methyl-4-isothiazolin-3-one (MI), but only over the limited range of ratios of n-BBIT to MI of 10:1 to 1.67:1. However, there is a need for additional combinations of antimicrobial compounds having enhanced activity against various strains of microorganisms to provide effective control of the microorganisms that is both quick and long lasting. Moreover, there is a need for combinations containing low levels of halogenated antimicrobial compounds. The problem addressed by this invention is to provide such additional combinations of antimicrobial compounds.

STATEMENT OF THE INVENTION

The present invention is directed to an antimicrobial composition comprising: (a) N-(n-butyl)-1,2-benzisothiazolin-3-one; and (b) 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one.

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The present invention is further directed to an antimicrobial composition comprising: (a) N-(n-butyl)-1,2-benzisothiazolin-3-one; and (b) a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, in a weight ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one up to 4:1.

DETAILED DESCRIPTION OF THE INVENTION

"MI" is 2-methyl-4-isothiazolin-3-one, also referred to by the name 2-methyl-3-isothiazolone. "CMI" is 5-chloro-2-methyl-4-isothiazolin-3-one. "DCOIT" is 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one. "n-BBIT" is N-(n-butyl)-1,2-benzisothiazolin-3-one.

As used herein, the following terms have the designated definitions, unless the context clearly indicates otherwise. The term " antimicrobial compound" refers to a compound capable of inhibiting the growth of or controlling the growth of microorganisms at a locus; antimicrobial compounds include bactericides, bacteristats, fungicides, fungistats, algaecides and algistats, depending on the dose level applied, system conditions and the level of microbial control desired. The term "microorganism" includes, for example, fungi (such as yeast and mold), bacteria and algae. The term "locus" refers to an industrial system or product subject to contamination by microorganisms. The following abbreviations are used throughout the specification: ppm = parts per million by weight (weight/weight), mL = milliliter, ATCC = American Type Culture Collection, and MIC = minimum inhibitory concentration. Unless otherwise specified, temperatures are in degrees centigrade (°C), and references to percentages (%) are by weight. Percentages of antimicrobial compounds in the composition of this invention are based on the total weight of active ingredients in the composition, i.e., the antimicrobial compounds themselves, exclusive of any amounts of solvents, carriers, dispersants, stabilizers or other materials which may be present. "Salt-free" means that the composition contains zero or up to 0.5%, preferably zero or up to 0.1%, and more preferably zero or up to 0.01%, of metal salt, based on weight of the composition.

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The compositions of the present invention unexpectedly have been found to provide enhanced antimicrobial efficacy at a combined active ingredient level lower than that of the individual antimicrobial compounds. In one embodiment of the invention, those antimicrobial compositions which contain halogenated 3-isothiazolones contain relatively low levels thereof, preferably no more than 5%, more preferably no more than 2%, and most preferably no more than 1.2%. Another preferred level is no more than 0.5%, and another is no more than 0.1%. Antimicrobial compositions dependent on the presence of halogenated 3-isothiazolone are susceptible to chemical degradation and may require additional stabilizer components, such as the aforementioned metal salt stabilizers; salt stabilizers sometimes create unacceptable properties in finished formulations. For this reason it is desirable to provide antimicrobial formulations substantially free of halogenated 3-isothiazolone, but that still provide the degree of antimicrobial protection provided by the halogenated 3-isothiazolones. In one embodiment of the invention, the total level of all halogenated antimicrobial compounds is no more than 5%, more preferably no more than 2%, more preferably no more than 1.2%. Another preferred level is no more than 0.5%, and another is no more than 0.1%.

In one embodiment of the invention, the antimicrobial composition comprises N-(n-butyl)-1,2-benzisothiazolin-3-one; 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one. The 2-methyl-4-isothiazolin-3-one and the 5-chloro-2-methyl-4-isothiazolin-3-one may be present in any ratio. A preferred composition contains 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a ratio up to 4:1; a commercial product contains these compounds in a ratio of about 3:1. In one preferred embodiment, the ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one is from 4:1 to 1:1.

In one embodiment of the invention, the antimicrobial composition comprises N-(n-butyl)-1,2-benzisothiazolin-3-one and 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one. Preferably, a weight ratio of N-(n-butyl)-1,2-benzisothiazolin-3-one to 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one is from 6000:1 to 30:1. Another preferred weight ratio is from 3000:1 to 35:1, another is from 300:1 to 30:1, and another from 300:1 to 35:1.

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In one embodiment of the invention, the antimicrobial composition comprises a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a weight ratio up to 4:1, respectively. Preferably, a weight ratio of N-(n-butyl)-1,2-benzisothiazolin-3-one to said mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one is from 12,000:1 to 50:1. Another preferred weight ratio is from 7500:1 to 60:1, another is from 900:1 to 100:1, and another from 300:1 to 100:1. In one embodiment of the invention, the weight ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one is approximately 3:1.

The antimicrobial compounds in the composition of this invention may be used "as is" or may first be formulated with a solvent or a solid carrier. Suitable solvents include, for example, water; glycols, such as ethylene glycol, propylene glycol, diethylene glycol, dipropylene glycol, polyethylene glycol, and polypropylene glycol; glycol ethers; alcohols, such as methanol, ethanol, propanol, phenethyl alcohol and phenoxypropanol; ketones, such as acetone and methyl ethyl ketone; esters, such as ethyl acetate, butyl acetate, triacetyl citrate, and glycerol triacetate; carbonates, such as propylene carbonate and dimethyl

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carbonate; and mixtures thereof. It is preferred that the solvent is selected from water, glycols, glycol ethers, esters and mixtures thereof. Suitable solid carriers include, for example, cyclodextrin, silicas, diatomaceous earth, waxes, cellulosic materials, alkali and alkaline earth (e.g., sodium, magnesium, potassium) metal salts (e.g., chloride, nitrate, bromide, sulfate) and charcoal.

When an antimicrobial component is formulated in a solvent, the formulation may optionally contain surfactants. When such formulations contain surfactants, they are generally in the form of emulsive concentrates, emulsions, microemulsive concentrates, or microemulsions. Emulsive concentrates form emulsions upon the addition of a sufficient amount of water. Microemulsive concentrates form microemulsions upon the addition of a sufficient amount of water. Such emulsive and microemulsive concentrates are generally well known in the art; it is preferred that such formulations are free of surfactants. U.S. Patent No. 5,444,078 may be consulted for further general and specific details on the preparation of various microemulsions and microemulsive concentrates.

An antimicrobial compound also can be formulated in the form of a dispersion. The solvent component of the dispersion can be an organic solvent or water, preferably water. Such dispersions can contain adjuvants, for example, co-solvents, thickeners, anti-freeze agents, dispersants, fillers, pigments, surfactants, biodispersants, sulfosuccinates, terpenes, furanones, polycations, stabilizers, scale inhibitors and anti-corrosion additives.

The antimicrobial compounds may be formulated separately or together. When both antimicrobial compounds are each first formulated with a solvent, the solvent used for the first antimicrobial compound may be the same as or different from the solvent used to formulate the other commercial antimicrobial compound. It is preferred that the two solvents are miscible. In the alternative, the first antimicrobial compound and the other antimicrobial compound may be combined directly and then a solvent added to the mixture.

Those skilled in the art will recognize that the antimicrobial compounds of the present invention may be added to a locus sequentially, simultaneously, or may be combined before being added to the locus. It is preferred that the first

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antimicrobial compound and the second antimicrobial compound be added to a locus simultaneously or combined prior to being added to the locus. When the antimicrobial compounds are combined prior to being added to a locus, such combination may optionally contain adjuvants, such as, for example, solvent, thickeners, anti-freeze agents, colorants, sequestrants (such as ethylenediamine-tetraacetic acid, ethylenediaminedisuccinic acid, iminodisuccinic acid and salts thereof), dispersants, surfactants, biodispersants, sulfosuccinates, terpenes, furanones, polycations, stabilizers, scale inhibitors and anti-corrosion additives.

The antimicrobial compositions of the present invention can be used to inhibit the growth of microorganisms by introducing an antimicrobially effective amount of the compositions onto, into, or at a locus subject to microbial attack. Suitable loci include, for example: cooling towers; air washers; mineral slurries; wastewater treatment; ornamental fountains; reverse osmosis filtration; ultrafiltration; ballast water; evaporative condensers; heat exchangers; pulp and paper processing fluids; plastics; emulsions; dispersions; paints; latices; coatings, such as varnishes; construction products, such as mastics, caulks, and sealants; construction adhesives, such as ceramic adhesives, carpet backing adhesives, and laminating adhesives; industrial or consumer adhesives; photographic chemicals; printing fluids; household products, such as bathroom and kitchen cleaners; cosmetics; toiletries; shampoos; soaps; detergents; industrial cleaners; floor polishes; laundry rinse water; metalworking fluids; conveyor lubricants; hydraulic fluids; leather and leather products; textiles; textile products; wood and wood products, such as plywood, chipboard, flakeboard, laminated beams, oriented strandboard, hardboard, and particleboard; petroleum processing fluids; fuel; oilfield fluids, such as injection water, fracture fluids, and drilling muds; agriculture adjuvant preservation; surfactant preservation; medical devices; diagnostic reagent preservation; food preservation, such as plastic or paper food wrap; pools; and spas.

Preferably, the antimicrobial compositions of the present invention are used to inhibit the growth of microorganisms at a locus selected from one or more of emulsions, dispersions, paints, latices, household products, cosmetics, toiletries, shampoos, soaps, detergents, machining fluids and industrial cleaners.

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In particular, the antimicrobial compositions are useful in emulsions, dispersions, paints and latices.

When the synergistic compositions of the present invention are used in personal care compositions, the formulated compositions may also comprise one or more ingredients selected from UV radiation-absorbing agents, surfactants, rheology modifiers or thickeners, fragrances, moisturizers, humectants, emollients, conditioning agents, emulsifiers, antistatic aids, pigments, dyes, tints, colorants, antioxidants, reducing agents and oxidizing agents.

The specific amount of the composition of this invention necessary to inhibit or control the growth of microorganisms in a locus depends upon the particular locus to be protected. Typically, the amount of the composition of the present invention to control the growth of microorganisms in a locus is sufficient if it provides from 0.1 to 10,000 ppm active ingredient of the composition in the locus. It is preferred that the active ingredients of the composition be present in the locus in an amount of at least 0.5 ppm, more preferably at least 1 ppm, more preferably at least 10 ppm and most preferably at least 50 ppm. It is preferred that the active ingredients of the composition be present in the locus in an amount of no more than 5000 ppm, more preferably no more than 3000 ppm, more preferably no more than 1000 ppm, and most preferably no more than 500 ppm.

EXAMPLES

The synergism of the combination of the present invention was demonstrated by testing a wide range of concentrations and ratios of the compounds.

One measure of synergism is the industrially accepted method described by Kull, F.C.; Eisman, P.C.; Sylwestrowicz, H.D. and Mayer, R.L., in Applied Microbiology 9:538-541 (1961), using the ratio determined by the formula:

$$Q_a/Q_A + Q_b/Q_B = \text{Synergy Index ("SI")}$$

wherein:

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Q_A = concentration of compound A (first component) in ppm, acting alone, which produced an end point (MIC of Compound A).

Q_a = concentration of compound A in ppm, in the mixture, which produced an end point.

Q_B = concentration of compound B (second component) in ppm, acting alone, which produced an end point (MIC of Compound B).

Q_b = concentration of compound B in ppm, in the mixture, which produced an end point.

When the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated, and when less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. The minimum inhibitory concentration (MIC) of an antimicrobial compound is the lowest concentration tested under a specific set of conditions that prevents the growth of added microorganisms.

Synergy tests were conducted using standard microtiter plate assays (12 columns, 1-12 x 8 rows, A-H) with media designed for optimal growth of the test microorganism. Full-strength nutrient medium, Trypticase Soy Broth, TSB, for bacteria, or Potato Dextrose Broth, PDB, for fungi, was used for testing. Growth medium (160 µL) was dispensed into columns 2-6 and 8-12 of the plate. A total of 40 plates were made with each growth medium. Stock solutions of N-(n-butyl)-1,2-benzisothiazolin-3-one were made from DENSIL DG 20 (20% active ingredient (AI), n-BBIT, in propylene glycol, obtained from Avecia Inc.) at the following concentrations based on total product weight: 5000 ppm (0.2 g DENSIL DG 20 in 40 g growth medium), 4000 ppm, 3500 ppm, 3000 ppm, 2500 ppm, 2000 ppm, 1500 ppm, 1000 ppm and 900 ppm. Isothiazolone stock solutions were made as follows. KATHON LX (1.97% active, 3:1 CMI/MI mixture): active ingredient concentrations at 144 ppm, 36 ppm, 10 ppm, 5 ppm and 1 ppm. ROZONE 2000 (20% active, DCOIT): active ingredient concentrations at 144 ppm, 36 ppm, 10 ppm, 5 ppm and 1 ppm. ROCIMA 550 (9.5% active, MI): active ingredient concentrations at 4800 ppm, 2400 ppm, 900 ppm, 360 ppm and 180

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ppm. DENSIL DG 20 stock solution was dispensed in each well of columns 1 and 7 of a microtiter plate, as described below:

1A, 7A – 4000 ppm stock	1E, 7E – 2000 ppm
1B, 7B – 3500 ppm	1F, 7F – 1500 ppm
1C, 7C – 3000 ppm	1G, 7G – 1000 ppm
1D, 7D – 2500 ppm	1H, 7H – 900 ppm

5000 ppm of stock solution was tested against *Ps. aeruginosa* in 1A, 7A. The 900 ppm stock was not tested against this organism. A 40 µL aliquot was transferred from each well in column 1 to column 2 and serially diluted to column 5; the aliquots from column 5 was discarded. Column 6 was the control. The same procedure was repeated from column 7 to column 11, and the aliquots from column 11 discarded. At the end of this procedure, each well should contain 160 µL of solution.

The isothiazolone stock solutions were added to various columns so that each well contained the desired concentration of the isothiazolone and the DENSIL DG20. The DENSIL DG20 alone as well as the isothiazolone alone were included as controls. An example of the combination of 11 ppm KATHON LX 1.5% (on an active ingredient basis) with DENSIL DG20 is shown below:

Concentrations of DENSIL DG20 and CMI/MI

	1	2	3	4	5	6	7	8	9	10	11	12
A	3556	711.1	142.2	28.4	5.7	0	3556/11	711/11	142/11	211/11	5.7/11	0/11
B	3111	622.2	124.4	24.9	5.0	0	3111/11	622/11	124/11	25/11	5/11	0/11
C	2667	533.3	106.7	21.3	4.3	0	2667/11	533/11	107/11	21/11	4.3/11	0/11
D	2222	444.4	889	17.8	3.6	0	2222/11	444/11	89/11	18/11	3.6/11	0/11
E	1778	355.6	71.1	14.2	2.8	0	1778/11	356/11	71/11	14/11	2.8/11	0/11
F	1333	266.7	53.3	10.7	2.1	0	1333/11	267/11	53/11	11/11	2.1/11	0/11
G	889	177.8	35.6	7.1	1.4	0	889/11	178/11	36/11	7/11	1.4/11	0/11
H	800	160	32	6.4	1.28	0	800/11	160/11	32/11	6.4/11	1.3/11	0/11

DENSIL DG20 alone (columns 1-5); untreated control (column 6); combination evaluations (columns 7-11); KATHON LX 1.5% control (column 12).

Inoculum (10 µL) was dispensed into each well from column 1-12. The plates were incubated (bacterial plates at 48 hrs., 30°C; fungal plates at 7 days, 25°C).

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The MIC of each biocide was determined from the plates, and then SI was determined.

The following concentrations of the isothiazolones with DENSIL DG20, as described above in the microtiter plate in columns 1-5, were evaluated:

CMI/MI and DCOIT	MI
11.2	400
8.8	300
6.4	200
4.8	160
4	133
2	107
1	80
0.5	67
0.35	60
0.28	50
0.13	40
0.06	30
0.03	25
	20
	16
	10
	5

Concentrations of the anti-microbial agents evaluated may vary slightly against different test organisms depending on their efficacy (lower concentrations against bacteria were used if the agent was more effective against bacteria. On the contrary, higher concentrations were needed in the test if the agent was less effective against bacteria).

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The following Tables summarize data for combinations of n-BBIT with other isothiazolones (ITA), along with their synergy index (SI) and the ratio of n-BBIT:ITA. All amounts of n-BBIT and ITA are reported as ppm of active ingredient. Results for testing against various organisms are grouped with results against fungi (F) reported together, and then results against bacteria (B).

	Alone			Combinations					Ratio
	ITA	ITA ppm	n-BBIT ppm	ITA ppm	n-BBIT ppm	Organisms	Contact Time	S.I.	n-BBIT:ITA
F	CMI/MI	1	28	0.03	25	*A. niger*	3 days	0.9	833:1
				0.06	25			0.9	417:1
				0.13	18			0.8	139:1
				0.28	18			0.9	64:1
				0.5	28			1.5	56:1
		0.28	444	0.03	356	*F. moniliforme*	3 days	0.9	11867:1
				0.06	356			1.0	5933:1
				0.13	267			1.1	2054:1
		1	533	0.06	444		7 days	0.9	7400:1
				0.28	267			0.8	954:1
				0.5	178			0.8	356:1
				0.03	533			1.1	17767:1
				0.13	533			1.0	4100:1
B	CMI/MI	5	267	1	178	*K. pneumoniae*	24 hr	0.9	178:1
				0.5	267			1.1	534:1
		11	267	1	178		48 hr	0.8	178:1
				2	178			0.8	89:1
		5	356	0.3	71	*E. coli*	24 hr	1.1	237:1
				0.5	53			0.9	106:1
				1	89			1.4	89:1
		5	533	0.1	89		48 hr	0.9	890:1
				0.3	89			0.9	297:1
				0.5	71			0.8	142:1
				1	107			1.2	107:1
				2	89			1.2	45:1

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	Alone			Combinations					Ratio
	ITA	ITA ppm	n-BBIT ppm	ITA ppm	n-BBIT ppm	Organisms	Contact Time	S.I.	n-BBIT: ITA
F	DCOIT	0.28	267	0.03	178	*F. moniliforme*	3 days	0.8	5933:1
				0.06	178			0.8	2967:1
				0.13	160			1.1	1231:1
				0.28	142			1.5	507:1
		1	356	0.06	267		7 days	0.8	4450:1
				0.13	267			0.9	2054:1
				0.5	124			0.8	248:1
				1	36			0.8	36:1
				0.03	356			1.0	11867:1
				0.28	356			1.3	1271:1
B	DCOIT	6	36	0.1	32	*S. aureus*	24 hr	0.9	320:1
				0.3	36			1.1	120:1
		9	53	0.3	36		48 hr	0.7	120:1
				0.5	53			1.1	106:1
				1	36			0.8	36:1
				2	53			1.2	27:1
		11	267	0.5	267	*K. pneumoniae*	48 hr	1.0	534:1
				1	178			0.8	178:1
				2	178			0.8	89:1
				4	267			1.4	67:1
		5	18	0.1	14	*P. mirabilis*	48 hr	0.9	140:1
				1	14			1.0	14:1
				0.3	18			1.1	60:1

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	Alone			Combinations					Ratio
	ITA	ITA ppm	n-BBIT ppm	ITA ppm	n-BBIT ppm	Organisms	Contact Time	S.I.	n-BBIT: ITA
F	MI	200	53	50	36	*A. niger*	7 days	0.9	1:1.4
				60	32			0.9	1:1.9
				107	18			0.9	1:5.9
				133	11			0.9	1:12
				160	7			0.9	1:23
				80	32			1.0	1:2.5
				200	7			1.1	1:29
		200	267	50	53	*F. moniliforme*	3 days	0.4	1.1:1
				60	56			0.4	1:1.1
				80	32			0.5	1:2.5
				107	36			0.7	1:3
				133	7			0.7	1:19
				160	5			0.8	1:32
		200	267	50	52		7 days	0.4	1:1
				60	36			0.4	1:1.7
				80	32			0.5	1:2.5
				107	32			0.7	1:3.3
				133	11			0.7	1:12
				160	6			0.8	1:27
				160	53			1.0	1:3
		107	711	50	142	*G. viridie*	3 days	0.7	2.8:1
				60	160			0.8	2.7:1
				80	142			0.9	1.8:1
		133	>711	50	160		7 days	<0.6	3.2:1
				60	160			<0.7	2.7:1
				80	160			<0.8	2:1
				107	178			<1.1	1.7:1
		25	124	10	53	*C. albicans*	7 days	0.8	5.3:1
				16	53			1.1	3.3:1
B	MI	20	711	5	444	*Ps. aeruginosa*	24 hr	0.8	89:1
		25	711	5	444		48 hr	0.8	89:1
				10	444			1.0	44:1
				16	533			1.4	33:1
		25	267	5	178	*K. pneumoniae*	24 hr	0.9	36:1
				10	107		48 hr	0.8	11:1
				16	89			1.0	5.6:1
				20	107			1.2	5.4:1

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Ps. aeruginosa - *Pseudomonas aeruginosa* (ATCC#15442)
S. aureus - *Staphylococcus aureus* (ATCC#6538)
K. pneumoniae - *Klebsiella pneumoniae* (ATCC#13583)
E. coli - *Escherichia coli* (ATCC#8739)
P. mirabilis - *Proteus mirabilis* (ATCC#unknown)

Fungi

A. niger - *Aspergillus niger* (ATCC#16404)
F. moniliforme - *Fusarium moniliforme* (ATCC#58929)
G. viridie (*T. viridie*) - *Gliocladium viridie* (*Tricoderma viridie*) (isolate)
C. albicans - *Candida albicans* (ATCC#10231)

Typical contact time for bacteria is 24 - 48 hours and 3 - 7 days for fungi.

Bacterial inoculum was approximately 1 x 10^6 to 1 x 10^7 cfu/ml per well of the microtiter plate.

Fungal inoculum was approximately 1 x 10^5 to 1 x 10^6 cfu/ml per well of the microtiter plate.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An antimicrobial composition comprising:
   (a) N-(n-butyl)-1,2-benzisothiazolin-3-one; and
   (b) 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one.

2. The antimicrobial composition of claim 1 in which a weight ratio of N-(n-butyl)-1,2-benzisothiazolin-3-one to 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one is from 6000:1 to 30:1.

3. The antimicrobial composition of claim 2 in which a weight ratio of N-(n-butyl)-1,2-benzisothiazolin-3-one to 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one is from 300:1 go 35:1.

4. An antimicrobial composition comprising:
   (a) N-(n-butyl)-1,2-benzisothiazolin-3-one; and
   (b) a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, in a weight ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one up to 4:1.

5. The antimicrobial composition of claim 4 in which a weight ratio of N-(n-butyl)-1,2-benzisothiazolin-3-one to said mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one is from 12,000:1 to 50:1.

6. The antimicrobial composition of claim 5 in which the composition contains no more than 2% of halogenated antimicrobial compounds.

7. The antimicrobial composition of claim 6 in which a weight ratio of 5-chloro-2-methyl-4-isothiazolin-3-one to 2-methyl-4-isothiazolin-3-one is from 4:1 to 1:1.

8. An antimicrobial composition according to claim 1 or 4, substantially as hereinbefore described with reference to the Examples.