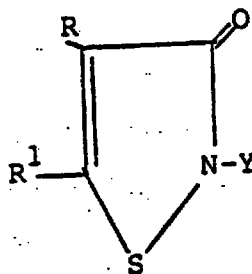


Description

This invention is concerned with stable compositions of 3-isothiazolones, their preparation, and their use in controlling living organisms. The isothiazolones which are stabilized include those disclosed in US-A-3,523,121 and US-A-3,761,488 as represented by the following structural formula:



I

wherein
Y

is an alkyl of from 1 to 18 carbon atoms optionally substituted with one or more hydroxy, halo, cyano, alkylamino, dialkylamino, arylamino, carboxy, carbalkoxy, alkoxy, aryloxy, alkylthio, arylthio, isothiazolonyl, haloalkoxy, carbamoxyl, morpholino, piperidino or pyrrolidino groups; alkenyl or alkynyl of from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, optionally substituted with one or more halo atoms; a cycloalkyl of from 5 to 8 carbon atoms, aralkyl optionally substituted with one or more halo, nitro, (C₁-C₄)alkyl or (C₁-C₄)alkoxy groups; or aryl optionally substituted with one or more halo, cyano, nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy (C₁-C₄)alkyl-acylamino, (C₁-C₄)carbalkoxy or sulfamyl groups;

R is hydrogen, halo, or (C₁-C₄)alkyl and R¹ is hydrogen, halo or (C₁-C₄)alkyl.

Representative Y substituents include methyl, ethyl, propyl, isopropyl, butyl, hexyl, octyl, cyclohexyl, benzyl, 3,4-dichlorobenzyl, 4-methoxybenzyl, 4-chlorobenzyl, 3,4-dichlorophenyl, 4-methoxyphenyl, hydroxymethyl, chloromethyl and chloropropyl.

Preferred isothiazolones are 5-chloro-2-methyl-3-isothiazolone, 2-methyl-3-isothiazolone, 2-octyl-3-isothiazolone, 4,5-dichloro-2-cyclohexyl-3-isothiazolone and 4,5-dichloro-2-octyl-3-isothiazolone.

Japanese Patent 1,318,306 discloses stabilizing a mixture of an isothiazolone and 2-hydroxymethyl-2-nitro-1,3-propanediol with a diol solvent. However, 2-hydroxymethyl-2-nitro-1,3-propanediol is a formaldehyde releaser, which is known to stabilize isothiazolones (see US-A-4,165,318 and US-A-4,129,448).

EP-A-208488 discloses the use of urea to stabilize isothiazolone solutions against the precipitation out of the isothiazolone, which is a particular problem when the isothiazolone is in the form of a salt.

European Patent Application 194,146 discloses stabilizing isothiazolones in non-aqueous, salt-free systems by several hydroxylic solvents, outstanding among them dipropylene glycol, whilst EP-A-166611 discloses stabilization by similar hydroxy solvents in systems containing small amounts of water and reduced stabilization salt.

Thus, until now, stabilization of isothiazolones against thermal degradation or storage degradation has generally been by metal salts, formaldehyde or formaldehyde releasers.

Both formaldehyde or formaldehyde-releasers and salt stabilization of isothiazolones have some drawbacks. Formaldehyde is a suspected carcinogen, and it is desirable not to use formaldehyde in applications where contact with human skin or lungs may occur.

This invention is directed to stable biocidal isothiazolone compositions in which (1) water may be substantially eliminated, (2) salt neutralization may be eliminated and (3) the need for nitrate stabilizer salts may be substantially eliminated.

This is achieved by the use of orthoesters having the following general formula:



II

wherein

X

is hydrogen, alkyl, for example alkyl of from 1 to 18 carbon atoms, or a substituted oxy of the formula OR^2 wherein R^2 is as defined below, or aryl, for example mononuclear aryl such as phenyl;

R^2 , R^3 and R^4

are the same or different radicals selected from alkyl, for example, alkyl of from 1 to 18 carbon atoms such as methyl, ethyl, propyl, butyl and octyl, and preferably (C_1-C_5) -alkyl, cycloalkyl, for example cycloalkyl of from 3 to 7 nuclear carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, aryl, for example, mononuclear aryl of from 6 to 10 carbon atoms such as phenyl;

alkylaryl, for example (C_1-C_6) alkyl-substituted mononuclear aryl such as methylphenyl and dimethylphenyl; or arylalkyl for example, mononuclear arylalkyl such as benzyl and phenethyl.

The preferred orthoesters of this invention are those wherein R^2 , R^3 and R^4 are all (C_1-C_5) alkyl and X is hydrogen, (C_1-C_5) alkyl or aryl. Especially preferred are trimethyl orthoformate, triethyl orthoformate, triethyl orthoacetate, trimethyl orthovalerate, and trimethyl orthobenzoate.

This invention extends to compositions which contain from about 0.1 to about 99.9 parts of one or more isothiazolones and an effective amount of an orthoester of Formula II (supra), preferably, an orthoester in the range of 0.1 to about 99.9 parts by weight.

More preferably, the composition comprises at least one isothiazolone wherein Y is (C_1-C_{18}) alkyl or (C_3-C_{12}) cycloalkyl; R is hydrogen or halo; and R^1 is hydrogen or halo. Typical formulation ranges are illustrated in the following Table (all percentages are by weight) for both a concentrated solution of the isothiazolone and a dilute solution. For certain uses, such as shipping of large quantities, more concentrated solutions may also be utilized.

FORMULATIONS TABLE		
Isothiazolone (I, Supra)	ORTHOESTER (II, Supra)	Solvent
0.1 - 99.9%	0.1% - 99.9%	0 - 99.8%
Preferred		
1 - 50%	1 - 25%	25 - 98%
More Preferred		
1 - 25%	1 - 10%	30 - 98%

When it is desired to package the isothiazolone with only the stabilizer and no other organic solvent or water present the amount of stabilizer or mixture of stabilizers employed will be from 1 percent to 25 percent. The isothiazolone may be present in a bulk form or packaged or encapsulated in some manner, including a form for controlled release. The weight ratio of orthoester to isothiazolone is preferably from about 1:7 to about 1.5:1.

Solvents other than orthoesters may be used to dissolve the isothiazolone and may be any organic solvent which dissolves the isothiazolones, is compatible with the proposed end use, does not destabilize the isothiazolone, and does not react with the orthoester to eliminate its stabilizing action.

Hydroxylic solvents, for example, polyols such as glycols, or alcohols, may be used. Under conditions of high dilution and high ratios of stabilizer to isothiazolone, glycols may be successfully used.

Preferred solvents are capped polyols, wherein the free hydroxy is replaced with an ether or ester function. Especially preferred are 2,5,8,11-tetraoxadecane, commonly known as triethylene glycol dimethyl ether, and 4,7-dioxaundecanol-1 acetate, commonly known as diethylene glycol butyl ether acetate.

The amounts of orthoester employed will vary depending on use conditions and concentrations of the isothiazolone in the mixture. In more concentrated solutions, effective amounts of orthoester based on isothiazolone are in the weight ratios of from about 1:4 to about 1:2. Obviously higher amounts may be

used, but at additional cost. At low levels of dilution of the isothiazolone (such as from 1 to 2 percent isothiazolone in the solvent), the weight ratio of stabilizer to isothiazolone can range from 1:7 to 2:1.

This invention permits the stabilization of isothiazolones wherein the previously necessary stabilization salts are substantially reduced and even eliminated. Useful stabilization salts which can be employed are those disclosed in US-A-3,870,795 and US-A-4,067,878 and include stabilization salts selected from:

- 1) Metal nitrates, where the metal is barium, cadmium, calcium, chromium, cobalt, copper, iron, lead, lithium, magnesium, manganese, mercury, nickel, sodium, silver, strontium, tin, zinc and the like; and
- 2) Copper (2+) salts where the anion is halide, sulfate, nitrate, nitrite, acetate, chlorate, perchlorate, bisulfate, bicarbonate, oxalate, maleate, carbonate, or phosphate and the like.

Uses of these new organically stabilized biocides are typically at any locus subject to contamination by bacteria, fungi or algae. Typically loci are in aqueous systems such as water cooling, laundry wash water, oil systems such as cutting oils or at oil fields where microorganisms need to be killed or where their growth needs to be controlled.

The stabilized biocide compositions of this invention are advantageous over salt stabilized isothiazolones described in the art and are the biocides of choice where salts pose a problem. For example, certain emulsions upon the addition of salt may coagulate. The compositions of this invention avoid this problem and therefore can be used in emulsions such as photographic emulsions, coating emulsions, (e.g. paints) to form solid protective or decorative films; electronic circuitry, wood, metals, plastics, fibers, membranes, carpet backings, ceramics and the like where surfaces need to be coated or protected, adhesives, caulks, and sensitive emulsions.

In many salt stabilized biocide systems of the prior art there is a potential for solids formation caused by interactions with other salts in the system, interaction with certain salt forming organics, by the conversion to organic salts, or simply by incompatibility with the system. The stabilized biocide compositions of this invention would be preferred in those systems. Also, the compositions of this invention are useful in fuel systems such as diesel fuel, gasoline, kerosene and certain alcohols because they eliminate the possibility of salt deposits on component parts. Another reason for eliminating salts is to avoid an environment in which corrosion can occur. For example, chloride salts (among others) have a corrosive effect on many metals and are to be avoided where possible. In water treatment systems where low cation and anion levels are important, this is especially true. Those familiar with the art in various areas where biological growth needs to be controlled will quickly recognize those applications where significant reduction of or elimination of salts will be desired. In many cases it is necessary to eliminate interactions between the stabilizing salts and other components of the system or formulation components which otherwise could reduce the performance or value of such systems.

It is also recognized that the isothiazolone stabilizers used in this invention have other known applications. For example, orthoformates are known to serve as reactive scavengers for molecules containing -OH, -NH₂, -SH and other nucleophilic groups. A biocide formulation stabilized with an orthoformate would be particularly advantageous where the dual function of biocidal/biostatic activity and scavenging would lead to advantageous results.

Because isothiazolone biocides are so active, the low level required to achieve stabilization also makes them ideal when compared to many known biocides because at the low levels required they are not likely to interfere with other components in systems requiring protection or with systems upon which the protected systems will be applied.

Potential areas of general application include disinfectants, sanitizers, cleaners, deodorizers, liquid and powder soaps, skin removers, oil and grease removers, food processing chemicals, dairy chemicals, food preservatives, animal food preservatives, wood preservation, paint, lazzures, stains, mildewcides, hospital and medical antiseptics, metal working fluids, cooling water, air washers, petroleum production, paper treatment, paper mill slimicides, petroleum products, adhesives, textiles, pigment slurries, latexes, leather and hide treatment, petroleum fuel, laundry sanitizers, agricultural formulations, inks, mining, nonwoven fabrics, petroleum storage, rubber, sugar processing tobacco, swimming pools, cosmetics, toiletries, pharmaceuticals, chemical toilets, household laundry products, diesel fuel additives, waxes and polishes and many other applications where water and organic materials come in contact under conditions which allow the growth of undesired microorganisms.

In the stabilization of plastic articles, it is desirable to eliminate salts in the isothiazolones, as salts may contribute to deterioration of optical properties and/or increase water pickup and haze levels.

In some cosmetic formulations, it is also important to have low water and salt content. Eliminating nitrate salts avoids the possibility of nitrosamine formation with any amines present in the formulation. Removal of multivalent cations from the biocide may also eliminate the known possibility of creating physical incompatibility problems in certain cosmetic formulations caused by precipitation of salts or complexes.

It is known in the art that the performance of biocides can frequently be enhanced by combination with one or more other biocides. In fact, there have been numerous examples of synergistic combinations of biocides. Thus, other known biocides may be combined advantageously with the stabilized isothiazolones of this invention.

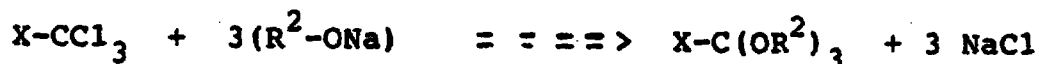
5 Isothiazolones are used as disinfectants, in oil field water treatment, as watercooling system micro-biocides, as preservatives for aqueous dispersions, emulsions or organic polymers, as wood pulp white water slimicides, as cosmetic preservatives, as cutting oil, jet fuel and as heating oil preservatives. Solutions of isothiazolones are also applied to a solid substrate, such as fabric, leather, paper or wood, as a preservative, or admixed with plastics.

10 The products of this invention are especially useful as preservatives for the following:

1. Cosmetics, as they eliminate or substantially reduce the presence of nitrates which under certain conditions in the presence of amines or amine precursors may lead to the formation of nitrosamines.
2. Oils and fuels, since added salts and moisture are eliminated or minimized thus preventing potential corrosion, deposition or sludge formation.
- 15 3. Emulsions and dispersions that are sensitive to the dispersions are those contained in a wide variety of products, such as paints, cosmetics, floor polishes and binders.
4. Plastics, as they eliminate or substantially reduce precipitated salts which can contribute directly or indirectly to haze, opacity, or physical weakness in the surface.

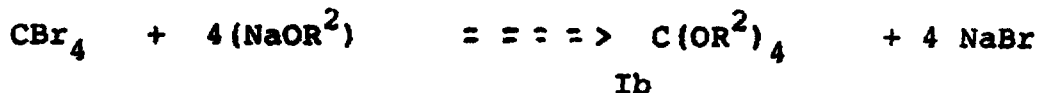
20 The term "orthoester" is well-known in the field of organic chemistry. They can also be named as ethers. Thus triethyl orthoacetate is named 1,1,1-trimethoxyethane, trimethyl orthobenzoate is tris(methoxy)-methylbenzene.

The orthoesters (I) of this invention are known compounds or may be prepared by methods well known to those skilled in the art. Thus symmetrical ($R^1 = R^2 = R^3$) orthoesters may be made by reacting a 1,1,1-trihalo compound with an appropriately substituted sodium oxide as illustrated by the following equations:

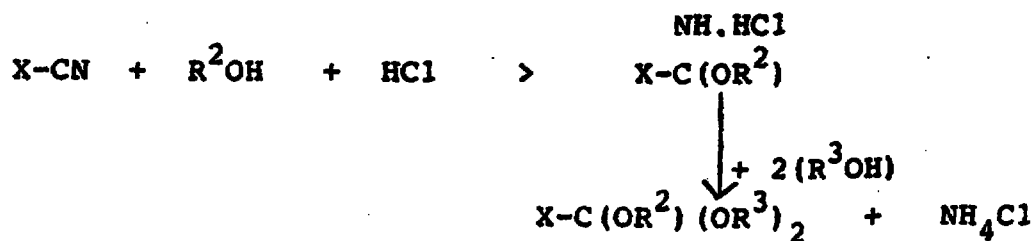


30 diethyl Ia
ether

Orthocarbonate esters may be prepared by a related method



40 Mixed orthoesters, ($R^2 \neq R^3$), may be prepared from the iminoether hydrochloride of the parent acid as illustrated by the following equations:



Ic

55 Derivatives of benzoic acid and related aromatic acids may be prepared by similar chemistry or by a controlled Grignard reaction on an orthocarbonate.



5

Id

Two especially useful compositions of the invention are those which (a) contain 14 percent by weight isothiazolone, or (b) contain 1.5 percent by weight isothiazolone, in both cases the isothiazolone preferably comprising one or more of 5-chloro-2-methyl-3-isothiazolone, 2-methyl-3-isothiazolone, 2-octyl-3-isothiazolone or 4,5-dichloro-2-octyl-3-isothiazolone.

The following examples in which all parts and percentages are by weight and all temperatures in degrees Centigrade, unless otherwise stated, are given for the purposes of illustration only.

For comparison of the stabilization of the compositions of this invention with known materials, the following tests were employed using a thermally-controlled solid metal block with bored holes as receptacles for the vials and with demonstrated temperature control, vials of stabilizer, solvent, and isothiazolone were made up and heated for fixed times. The percentage of the starting isothiazolone remaining was determined by high performance liquid chromatography (HPLC). Temperatures of 40°, 55°, and 70°C were used. Results were considered indicative of acceptable stability when remainder values indicated essentially no loss during the time specified for the isothiazolone or isothiazolone mixture studied.

I. Stability Test for 5-Chloro-2-methylisothiazolin-3-one/2-Methylisothiazolin-3-one

The 3:1 mixture of 5-chloro-2-methylisothiazolin-3-one/2-methylisothiazolin-3-one (16.2%) is mixed at 14% active ingredient (AI) in triglyme (76.8%) with the chosen stabilizer (7%). The retention of AI is measured after four weeks at 40°C and after one and two weeks at 70°C. HPLC is used to measure AI. Maintenance of AI must be >85% to meet the target of most preferred. Other stabilizers may be less effective in the test, but may be adequate for stabilization under shorter time, less exacerbated conditions. This is compared with a 3:1 mixture of 5-chloro-2-methylisothiazolin-3-one/2-methylisothiazolin-3-one stabilized with magnesium nitrate (15%).

The following results were obtained.

Ex. No.	Stabilizer	1 week, 70°	2 weeks, 70°	4weeks, 40°
1	None	F	F	32
2	Mg(NO ₃) ₂ , 15%	P	P	P
3	Trimethyl orthoformate (TOF)	P	P	P
4	Triethyl orthoformate (TEOF)	P	P	P
5	Triethyl orthoacetate (TOA)	P	P	P
6	Triethyl orthovalerate (TOV)	P	P	P
7	Tetramethyl orthocarbonate (TOC)	P	P	P
8	Trimethyl orthobenzoate (TOB)	P	P	P
(P indicates greater than 85% retention of AI. F indicates less than 10% retention, ie. complete and unacceptable loss of activity.)				

II. Ratios of Stabilizer to Isothiazolone

Data are here presented for weeks of stability at 55°. In all cases, AI was 14% of the mixed isothiazolone, the stabilizer was at percentages of from 0 to 7, and the remainder was the solvent. BCA = 4,7-dioxaundecanol-1-acetate; DPG = dipropylene glycol; TEOF = triethyl orthoformate; P and F are as defined earlier. (Some stability is offered by certain solvents in the absence of stabilizer, but not of commercially-acceptable magnitude.)

Ratio of Stabilizer to Isothiazolone at 14% AI						
Ex. No.	Stabilizer, %		Solvent	% AI Remaining After 55° C		
				2 weeks	4 weeks	8 weeks
9	TEOF	7	BCA	P	P	P
10	TEOF	5	BCA	P	P	P
11	TEOF	3	BCA	P	P	50
12	TEOF	1	BCA	50	15	F
13	None		BCA	55	40	15
14	TEOF	7	DPG	P	P	P
15	TEOF	5	DPG	P	P	P
16	TEOF	3	DPG	P	F	F
17	TEOF	1	DPG	F	F	F
18	None		DPG	F	F	F

Ratios of Stabilizer to Isothiazolone at 1.5% AI						
Ex. No.	Stabilizer, %		Solvent	% AI Remaining After 55° C		
				2 weeks	4 weeks	8 weeks
19	TEOF	2	BCA	P	P	P
20	TEOF	1	BCA	P	P	P
21	TEOF	0.5	BCA	P	P	P
22	TEOF	0.25	BCA	P	P	P
23	None		BCA	P	P	80
24	TEOF	2	DPG	P	P	P
25	TEOF	1	DPG	30	F	--
26	TEOF	0.5	DPG	F	F	--
27	TEOF	0.25	DPG	F	F	--
28	None		DPG	F	F	F

Example 29

The neat isothiazolone (Structure I $R^1 = Cl$, $R = H$, $Y = CH_3$; $R = R^1 = H$, $Y = CH_3$ (3:1)) was stabilized with 5% or 20% triethyl orthoformate. These were stored one week at 40° and 55° and compared with unstabilized neat isothiazolone. The retention of active ingredient is shown below.

Stabilizer	%	%AI Remaining After Storage for 1 week at	
		40°	55°
None	-	98.4	49.7
TEOF	5	100.0	99.7
TEOF	20	100.0	99.7

Example 30 - Hair Shampoo

A solution containing 1.5% of N-methyl-5-chloroisothiazolin-3-one and N-methylisothiazolin-3-one, and 2.0% of triethyl orthoformate as stabilizer in 96.5 dipropylene glycol is used as a preservative for a hair shampoo.

Example 31

Shown below is percent of 5-chloro-2-methyl isothiazolin-3-one stabilized with trimethyl orthoformate in various solvents remaining after 2 weeks at 70°C, where initial isothiazolone content was 14% and 7% stabilizer is used, the balance being the solvents listed.

Tetra-Glyme	Dipropylene Glycol	Propylene Glycol Methyl Ether Acetate	Diethylene Glycol Butyl Ether Acetate	Triacetin (glycol triacetate)	Ethylene Glycol Diacetate	DPG + 5% Water
100	94	100	99	97	97	0

Example 32

The advantage of eliminating salt shock in polymer emulsions is shown in the following example. Salt shock is observed as a precipitate or gelatinous mass that forms in the polymer emulsion when isothiazolone, containing stabilizers composed of divalent metal ions (e.g. Mg^{++} , Cu^{++}), is added as a preservative.

The polymer emulsion is initially passed through a 325 mesh screen to remove any gel that might be present from manufacture. Isothiazolone is added to a total amount of 30 ppm AI based on total polymer emulsion. A 250g. emulsion sample in a pint container is used. The sample is gently swirled after pipetting the appropriate amount of isothiazolone. The sample is inverted twice to mix and allowed to stand at ambient temperature for sixty minutes. The sample is again passed through a 325 mesh screen. Any gel or precipitate on the screen is washed with deionized water to remove residual, uncoagulated polymer emulsion. The material remaining on the screen is collected and dried overnight at 50°C. This is followed by heating 1 hour at 150°C to remove any remaining water. The residue is then weighed.

Gel Formation in Some Polymer Emulsions

	<u>Isothiazolone</u>	<u>Stabilizer</u>	<u>Weight Gel Recovered mg/Kg emulsion</u>
Emulsion 1	1.5% AI	{magnesium nitrate copper nitrate	2800, 2620
	1.5% AI	TEOF	16
Emulsion 2	1.5% AI	{magnesium nitrate copper nitrate	2520, 2424
	1.5% AI	TEOF	51

The small amount of gel formed when the emulsion is preserved with stabilized isothiazolone (<60mg/kg emulsion) will not be detrimental in the use of the emulsion in various applications such as paints, caulks, and the like. The amount of gel formed (>2400mg/kg emulsion) when salt stabilized isothiazolone is used as a preservative would be easily visible and objectionable.

Example 33

The following test was carried out to determine the microbial speed of kill of the orthoformate stabilized isothiazolone compared to the nitrate stabilized isothiazolone. This illustrated equivalent bactericidal activity when either the nitrate or orthoester stabilizer is used.

A. DESCRIPTION OF THE SPEED OF KILL TEST

This test measures bactericidal activity in water free of organic matter. It measures the loss of cell viability in an aqueous suspension of bacterial cells as a function of time when these cells are contacted with a defined concentration of test compound in the water. This is done by taking aliquots of the cell suspensions at the appropriate time interval and assaying the number of viable cells per milliliter by plate count or most probably number (MPN) methodology. These measurements are done on the cell suspen-

sions containing no test compound. The viable cell counts of the test and control samples are then compared to determine cell death.

The inoculum is prepared by growing the bacteria on a slant for 24 hours and then harvesting the cells into phosphate buffer. To start the test at zero time, one volume of bacterial inoculum is added to 100
5 volumes of test solution containing compound at the final test concentration.

At appropriate time intervals, such as 2, 4 and/or 24 hours, aliquots of all the test samples and controls are assayed for viable cell count, reported as most probable number (MPN) per ml.

The results are calculated in terms of log₁₀ reduction in MPN/ml compared to aqueous control. This is done by taking the logarithm base 10 of the MPN/ml for the test count and subtracting this number from the
10 logarithm base 10 of the MPN/ml for the aqueous control count. One log reduction corresponds to 90% kill, 2 logs reduction corresponds to 99% kill, 3 logs reduction corresponds to 99.9% kill, etc.

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Results From Speed of Kill Test

Active Ingredient = Structure I 3 parts ($R^1=ClR=H, Y=CH_3$)+1 part ($R^1=H, Y=CH_3$)

Sample #	AI	Stabilizer	Stabilizer	Solvent	SOK in synthetic hard water		SOK in Mg9 Medium	
					30 minutes	4hr	30 minutes	4hr
					5.00 log reduction			
1	14	TEOF	9	BCA	0/8	>5.00	250 ppm	32 ppm
2	14	TEOF	9	BCA	0/8	>5.00	250 ppm	32 ppm
3	14	magnesium nitrate	15	water	0/8	>5.00	250 ppm	32 ppm
4	1.5	TEOF	2	DPG	1/8	>5.00	250 ppm	32 ppm
5	1.5	magnesium nitrate copper nitrate	1.6 0.15	water	0/8	>5.00	250 ppm	32 ppm

Example 34

The minimum inhibitory concentration (MIC) of both nitrate stabilized and orthoformate stabilized isothiazolone was determined and found to be equivalent.

MINIMUM INHIBITORY CONCENTRATION TEST

A minimum inhibitory concentration (MIC) test is used to evaluate the antimicrobial activity of a test compound in preservative applications. The MIC value is obtained in the following manner. A volume of the stock solution containing 1% AI is dispensed into enrichment broth to give an initial starting test concentration of 250 ppm compound.

At the start of the test, each vessel in the dilution series, except the first vessel, contains an equal volume of the compound free broth. The first vessel contains twice the volume of broth with the starting concentration of test compound. One half of the broth from the first vessel is transferred to the second vessel. After being mixed, one half the resulting volume is removed from the second vessel and transferred to the third vessel. The entire cycle is repeated 8 to 12 times, depending on the number of dilutions desired. The result is a two-fold serial dilution of test compound in the enrichment broth.

Each vessel is then inoculated with a cell suspension of the appropriate test organism. Bacteria are grown in broth and fungi on agar slants, for a time and at a temperature appropriate to the species being tested. At the end of the growth period, the broth is vortexed to disperse the cells. In the case of fungi, the spores are harvested by pipetting water onto the slant and dislodging the spores with a sterile loop. The cell/spore suspensions are standardized by controlling incubation time and temperature and the volume of the diluent. Once inoculated, the vessels are incubated at the appropriate temperature, and then examined for growth/no growth. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of compound that results in complete inhibition of growth of the test organism.

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Minimum Inhibitory Concentration (ppm AI)

Active Ingredient = Structure I 3 parts ($R^1=Cl, R^2=H, Y=CH_3$) + 1 part ($R^1=R^2=H, Y=CH_3$)

Sample	SAI	Stabilizer	Stabilizer	Solvent	Microorganisms					
					Psfl	Psae	Saur	Ecol	Calb	Anig
1	14	TEOF	9	BCA	2	8/4	16	4	1	2
2	14	TEOF	9	BCA	2	4	16	8	2/1	2
3	14	magnesium nitrate	15	water	2	4	16	8	2	2
4	1.5	TEOF	2	DPG	2	8	16	4	2	2
5	1.5	magnesium nitrate	1.6	water	2	4	16	4	2	2/1
		copper nitrate	0.15							

Psfl = Pseudomonas fluorescens

Psal = Pseudomonas aeruginosa

Saur = Staphylococcus aureus

Ecol = Escherichia coli

Calb = Candida albicans

Anig = Aspergillus niger

Apul = Aureobasidium pullulans

Claims

1. A stabilized isothiazolone composition comprising an isothiazolone of the formula:



Minimum Inhibitory Concentration (ppm AI)

Active Ingredient = Structure I 3 parts ($R^1=Cl, R=H, Y=CH_3$) + 1 part ($R^1=R=H, Y=CH_3$)

Sample	AI	Stabilizer	Stabilizer	Solvent	Microorganisms					Calb	Anig	Apul
					Psfl	Psae	Saur	Ecol				
1	14	TEOF	9	BCA	2	8/4	16	4	1	2	1	
2	14	TEOF	9	BCA	2	4	16	8	2/1	2	1	
3	14	magnesium nitrate	15	water	2	4	16	8	2	2	1	
4	1.5	TEOF	2	DPG	2	8	16	4	2	2	2	
5	1.5	magnesium nitrate (copper nitrate 0.15)	1.6	water	2	4	16	4	2	2	2/1	

Psfl = Pseudomonas fluorescens

Psal = Pseudomonas aeruginosa

Saur = Staphylococcus aureus

Ecol = Escherichia coli

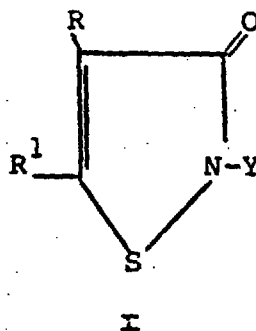
Calb = Candida albicans

Anig = Aspergillus niger

Apul = Aureobasidium pullulans

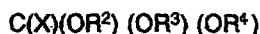
Claims

1. A stabilized isothiazolone composition comprising an isothiazolone of the formula:



wherein

Y is an alkyl of from 1 to 18 carbon atoms optionally substituted with one or more hydroxy, halo, cyano, alkylamino, dialkylamino, arylamino, carboxy, carbalkoxy, alkoxy, aryloxy, alkylthio, arylthio, isothiazolonyl, haloalkoxy, carbamoxy, morpholino, piperidino or pyrrolidino groups; alkenyl or alkynyl of from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, optionally substituted with one or more halo atoms; a cycloalkyl of from 5 to 8 carbon atoms, aralkyl optionally substituted with one or more halo, nitro, (C₁-C₄)alkyl or (C₁-C₄)alkoxy groups; or aryl optionally substituted with one or more halo, cyano, nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy (C₁-C₄)-alkyl-acylamino, (C₁-C₄)carbalkoxy or sulfamyl groups; and a stabilising amount of orthoester of the formula:



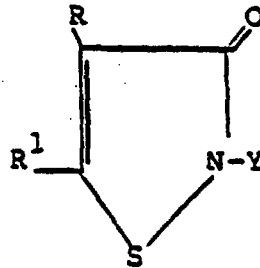
wherein X is hydrogen, (C₁-C₁₈)alkyl, OR⁵ or (C₆-C₁₀)aryl; R², R³, R⁴ and R⁵ are the same or different radicals selected from (C₁-C₁₈)alkyl, (C₃-C₇)cycloalkyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylaryl and mononuclear arylalkyl.

2. The composition of Claim 1 which also optionally contains organic solvent for the isothiazolone and the weight ratios of isothiazolone, orthoester and solvent and 0.1 to 99.9, 99.9 to 0.1 and 0 to 99.8 respectively.
3. A composition of Claim 2 which comprises from 1 to 50 parts of isothiazolone; from 1 to 25 parts of orthoester and from 25 to 98 parts of solvent, by weight.
4. A composition of Claim 3 which comprises from 1 to 25 parts of isothiazolone; from 1 to 10 parts of orthoester and from 30 to 98 parts of solvent, by weight.
5. A composition according to any preceding claim wherein Y is (C₁-C₁₈)alkyl or (C₃-C₁₂)cycloalkyl; R is hydrogen or halo; R¹ is hydrogen or halo, R², R³ and/or R⁴ are (C₁-C₅)-alkyl, and X is hydrogen, alkyl, or aryl.
6. A composition of any preceding claim in which the orthoester comprises one or more of trimethyl orthoformate, triethyl orthoformate, triethyl orthoacetate, trimethyl orthovalerate or trimethyl orthobenzoate.
7. A method of inhibiting the growth of bacteria, fungi, or algae in a locus subject to contamination thereby, said locus not being the human or animal body, which comprises incorporating onto or into the locus, an effective amount of a composition of any preceding claim.
8. A method of Claim 7 wherein the locus is an aqueous medium.
9. A method of Claim 7 wherein the locus is a cutting oil formulation, a water-cooling system, a solid protective or decorative film, fabric, leather, paper, or wood, laundry wash water, a cosmetic formulation, a fuel system, a plastics material or an emulsion.



Patentansprüche

1. Stabilisierte Isothiazolonzusammensetzung, enthaltend ein Isothiazolon der Formel:



in der Y eine Alkylgruppe ist mit 1-18 Kohlenstoffatomen, gegebenenfalls substituiert mit einer oder mehreren Hydroxy-, Halogen-, Cyano-, Alkylamino-, Dialkylamino-, Arylamino-, Carboxy-, Carbalkoxy-, Alkoxy-, Aryloxy-, Alkylthio-, Arylthio-, Isothiazolonyl-, Haloalkoxy-, Carbamoxy-, Morpholino-, Piperidino- oder Pyrrolidinogruppen; eine Alkenyl- oder Alkynylgruppe mit 2-8 Kohlenstoffatomen, vorzugsweise mit 2-4 Kohlenstoffatomen, gegebenenfalls substituiert mit einem oder mehreren Halogenatomen; eine Cycloalkylgruppe mit 5-8 Kohlenstoffatomen, eine Aralkylgruppe, gegebenenfalls substituiert mit einer oder mehreren Halogen-, Nitro-, (C₁-C₄)-Alkyl- oder (C₁-C₄)-Alkoxygruppen; oder Aryl, gegebenenfalls substituiert mit einer oder mehreren Halogen-, Cyano-, Nitro-, (C₁-C₄)-Alkyl-, (C₁-C₄)-Alkoxy-, (C₁-C₄)-Alkyl-Acylamino-, (C₁-C₄)-Carbalkoxy- oder Sulfamylgruppen, und eine stabilisierende Menge von Orthoester der Formel



in der X Wasserstoff, (C₁-C₁₈)-Alkyl, OR⁵ oder (C₆-C₁₀)-Aryl ist; R², R³, R⁴ und R⁵ gleiche oder unterschiedliche Gruppen sind, ausgewählt aus (C₁-C₁₈)-Alkyl, (C₃-C₇)-Cycloalkyl, (C₆-C₁₀)-Aryl, (C₁-C₆)-Alkylaryl und einkernigem Arylalkyl.

2. Zusammensetzung nach Anspruch 1, **dadurch gekennzeichnet,**

daß sie gegebenenfalls auch organisches Lösemittel für das Isothiazolon enthält und die Gewichtsverhältnisse von Isothiazolon, Orthoester und Lösemittel von 0,1-99,9, 99,9-0,1 bzw. 0-99,8 betragen.

3. Zusammensetzung nach Anspruch 2, **dadurch gekennzeichnet,**

daß sie von 1-50 Gewichtsteile Isothiazolon, von 1-25 Gewichtsteile Orthoester und von 25-98 Gewichtsteile Lösemittel enthält.

4. Zusammensetzung nach Anspruch 3, **dadurch gekennzeichnet,**

daß sie von 1-25 Gewichtsteile Isothiazolon, von 1-10 Gewichtsteile Orthoester und von 30-98 Gewichtsteile Lösemittel enthält.

5. Zusammensetzung nach jedem der vorstehenden Ansprüche, **dadurch gekennzeichnet,**

daß Y (C₁-C₁₈)-Alkyl oder (C₃-C₁₂)-Cycloalkyl ist; R Wasserstoff oder Halogen ist; R¹ Wasserstoff oder Halogen ist, R², R³ und/oder R⁴ (C₁-C₅)-Alkyl sind und X Wasserstoff, Alkyl oder Aryl ist.

6. Zusammensetzung nach jedem der vorstehenden Ansprüche, **dadurch gekennzeichnet,**

daß der Orthoester ein oder mehrere von Trimethylorthoformiat, Triethylorthoformiat, Triethylorthoacetat, Trimethylorthovalerat oder Trimethylorthobenzoat enthält.

7. Verfahren zum Hemmen des Wachstums von Bakterien, Pilzen oder Algen an einer damit verunreinig-

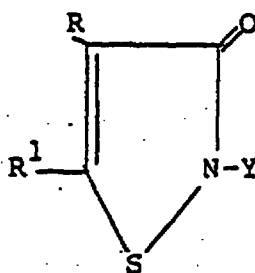


ten Stelle, wobei die Stelle kein menschlicher oder tierischer Körper ist, durch Einbringen auf oder in die Stelle einer wirksamen Menge einer Zusammensetzung nach jedem der vorstehenden Ansprüche.

8. Verfahren nach Anspruch 7,
dadurch gekennzeichnet,
daß die Stelle ein wäßriges Medium ist.
9. Verfahren nach Anspruch 7,
dadurch gekennzeichnet,
daß die Stelle eine Schneidölformulierung, ein Wasserkühlsystem, ein fester Schutz- oder dekorativer Film, Gewebe, Leder, Papier oder Holz, Wäschereispülwasser, eine kosmetische Formulierung, ein Brennstoffsystem, ein Kunststoff oder eine Emulsion ist.

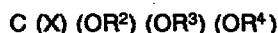
Revendications

1. Composition d'isothiazolone stabilisée, comprenant une isothiazolone de formule :



dans laquelle :

Y représente un groupe alkyle ayant 1 à 18 atomes de carbone éventuellement substitué par un ou plusieurs groupes hydroxy, halogéno, cyano, alkylamino, dialkylamino, arylamino, carboxy, carbalcoxy, alcoxy, aryloxy, alkylthio, arylthio, isothiazolonyle, halogéno-alcoxy, carbamoxo, morpholino, pipéridino ou pyrrolidino ; alcényle ou alcynyle ayant 2 à 8 atomes de carbone, de préférence 2 à 4 atomes de carbone éventuellement substitué par un ou plusieurs atomes d'halogène(s) ; un groupe cycloalkyle de 5 à 8 atomes de carbone arylalkyle éventuellement substitué par un ou plusieurs atomes d'halogène(s) ou groupes nitro, alkyle (en C₁ à C₄) ou alcoxy (en C₁ à C₄) ; ou aryle éventuellement substitué par un ou plusieurs atomes d'halogène(s) ou groupes cyano, nitro, alkyle (en C₁ à C₄), alcoxy (en C₁ à C₄) alkyl (en C₁ à C₄)-acylamino, carbalcoxy (en C₁ à C₄) ou sulfamyle ; et une quantité stabilisante d'un ortho-ester de formule :



dans laquelle X représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₁₈, OR⁵ ou aryle en C₆ à C₁₀ ; R², R³, R⁴ et R⁵ représentent des radicaux, identiques ou différents ; choisis parmi les alkyle en C₁ à C₁₈, cycloalkyle en C₃ à C₁₇, aryle en C₆ à C₁₀, alkylaryle en C₁ à C₆ et alylalkyle mononucléaire.

2. Composition selon la revendication 1, qui contient éventuellement aussi du solvant organique pour l'isothiazolone et dans laquelle les taux ou rapports pondéraux d'isothiazolone, de l'ortho-ester et du solvant sont respectivement de 0,1 à 99,9, de 99,9 à 0,1 et de 0 à 99,8.
3. Composition selon la revendication 2, qui comprend de 1 à 50 parties d'isothiazolone ; de 1 à 25 parties d'ortho-ester et de 25 à 98 parties de solvant, en poids.
4. Composition selon la revendication 3, qui comprend de 1 à 25 parties d'isothiazolone ; de 1 à 10 parties d'ortho-ester et de 30 à 98 parties de solvant, en poids.
5. Composition selon l'une quelconque des revendications précédentes dans laquelle Y représente un groupe alkyle en C₁ à C₁₈ ou cycloalkyle en C₃ à C₁₂ ; R représente un atome d'hydrogène ou



d'halogène ; R¹ représente un atome d'hydrogène ou d'halogène ; R², R³ et/ou R⁴ représentent chacun un groupe alkyle en C₁ à C₅, et X représente un atome d'hydrogène ou un groupe alkyle ou aryle.

- 5 6. Composition selon l'une quelconque des revendications précédentes, dans laquelle l'ortho-ester comprend un ou plusieurs des composés suivants : l'orthoformiate de triméthyle, l'orthoformiate de triéthyle, l'ortho-acétate de triéthyle, l'orthoalérate de triméthyle ou l'orthobenzoate de triméthyle.
- 10 7. Procédé pour inhiber la croissance de bactéries, de champignons ou d'algues dans un lieu sujet à une telle contamination, ledit lieu n'étant pas le corps d'un être humain ou d'un animal, ce procédé comprenant l'incorporation, sur ou dans le lieu, d'une quantité efficace d'une composition selon l'une quelconque des revendications précédentes.
8. Procédé selon la revendication 7, dans le cas duquel le lieu est un milieu aqueux.
- 15 9. Procédé selon la revendication 7, dans le cas duquel le lieu est une formulation d'huile de coupe, un système ou circuit de refroidissement par eau, une pellicule solide protectrice ou décorative, une étoffe, du cuir, du papier ou du bois, de l'eau de lavage pour lessive, une formulation cosmétique, un système ou circuit de carburant ou de combustible, une matière plastique ou une émulsion.

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