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(54) Title: COMPOSITION OF MATTER CONTAINING IMIDAZOLIDINYL UREA AND PYRITHIONE AND ITS DERIVATIVES (57) Abstract A composition of matter comprising a major part of imidazolidinyl urea and a minor part of pyrithione and/or one or more derivatives of pyrithione. The composition exhibits synergistic anti-microbial activity.		

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COMPOSITION OF MATTER CONTAINING
IMIDAZOLIDINYL UREA AND PYRITHIONE
AND ITS DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention is directed to a composition of matter which exhibits synergistic activity against contaminating microorganisms.

5 Pyrrithione, also identified as 2-mercapto-
pyridine-1-oxide and 1-hydroxypyridine-2-thione and
given CAS registry numbers 1121-30-8 and 1121-31-9, and
its derivatives are known to be active against a variety
of microorganisms. They, therefore, have been used in
10 a variety of products to inhibit contamination by micro-
organisms including cosmetics, lubricants, and water-
based paints. The most commonly used derivatives of
pyrrithione are the alkali metal and heavy metal salts,
principally the sodium and zinc salts. See, Nelson and
15 Hyde, "Sodium and Zinc Omadine® Antimicrobials as
Cosmetic Preservatives", Cosmetics & Toiletries, Vol. 96,
No. 3, p 87. However, other derivatives such as
pyrrithione disulfide and the magnesium sulfate adduct
thereof have also been proposed as antimicrobial agents.
20 Further details concerning the manufacture and use of
pyrrithione and its derivatives are found in United
States Patent No. 2,745,826 and British Patent Specifica-
tion No. 761,171, the disclosures of which are hereby
incorporated by reference.



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Imidazolidinyl urea is the name given to a bacteriocidal compound prepared as described in Example IV of United States Patent No. 3,248,285 (and hereby incorporated by reference) and has been given the CAS registry number 39236-46-9. This compound has been widely used to preserve cosmetics, agricultural products and foodstuffs, paints, lubricants, plastics and textiles from bacteria.

The present invention is predicated upon the discovery that a composition of matter based on the combination of imidazolidinyl urea and pyrithione and/or its derivatives exhibits synergistic activity against the microorganism *C. albicans*, a commonly occurring and problematic microbial. The composition, thus, provides a new and effective means for protecting perishable products from the harmful effects of contaminating microorganisms.

SUMMARY OF THE INVENTION

The composition of the invention comprises a major part of imidazolidinyl urea and a minor part of pyrithione and/or its derivatives. By the term major part is meant more than 50% by weight based upon the total weight of the imidazolidinyl urea and pyrithione components of the composition. Conversely, the term minor part means less than 50% by weight based upon the total weight of the imidazolidinyl urea and pyrithione components.

Particularly preferred compositions are those containing sodium or zinc pyrithione and imidazolidinyl urea.

The composition of the invention may be used to preserve a variety of liquid and solid products from microbial contamination including, but not limited to, lotions, creams, soaps, shampoos and hair conditioners, lubricants, plastics, agricultural products and foodstuffs, pharmaceutical products and medicaments.



DETAILED DESCRIPTION OF THE INVENTION

Since imidazolidinyl urea and pyrithione and its derivatives can be manufactured as powdered solids, the composition of the invention may be prepared as a powder by simply mixing the individual components together in the appropriate proportions. Alternatively, aqueous solutions can be prepared from imidazolidinyl urea, which is highly water soluble and the pyrithione derivatives which are also water soluble, such as sodium pyrithione. Aqueous dispersions may be prepared from non-water soluble pyrithiones, such as zinc pyrithione. Other solvents can be used to prepare liquid formulations of the composition as, for example, propylene glycol. Of course, the choice of solvent will depend upon the solubility characteristics of the particular pyrithione(s) used in the composition.

As shown in the following Table, the combination of a pyrithione and imidazolidinyl urea exhibits synergistic antimicrobial activity, in a challenge test using *Candida albicans* (ATCC 10231):

	<u>Test Solution</u>	<u>Concentration</u>	<u>Results on Subculture after 72 hour Incubation Period</u>
25	Imidazolidinyl urea	0.3%	+
		0.6%	+
	Sodium pyrithione	0.005%	+
		0.006%	+
30		0.007%	+
		0.008%	+
		0.010%	+
	Imidazolidinyl urea (0.3%)	}	0
	plus	}	
35	Sodium pyrithione (0.005%)	}	



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- + representing growth of micro-organisms on subculture (i.e., microbial survival in test solution)
- 5 0 representing no growth on subculture (i.e., complete kill in test solution)

The challenge test was conducted as follows:

1. 4.5ml of the undiluted compound was placed
10 into a 16 x 150mm test tube.
2. 0.5ml of a 24 hour Trypticase Soy Broth (TSB) culture was added to the compound.
3. The challenged compound was allowed to sit
15 at room temperature for 72 hours, after which a count was made on the sample to recover the viable cells, using standard pour plate procedure and trypticase soy agar pour plates. The remainder of the sample was added to 100ml of TSB for a sterility test.
4. All subculture media were incubated at 35°C
20 for 48 hours and then observed for growth.
5. All negative media were challenged with a low number of organisms to assure that the media was growth-promoting.

The challenge test demonstrates that although
25 0.6% imidazolidinyl urea or 0.01% sodium pyrithione failed to kill *C. albicans*, a mixture of half of each, i.e., 0.3% imidazolidinyl urea and 0.005% sodium pyrithione achieved a complete kill.

The actual microbial counts make clear that
30 the combination of imidazolidinyl urea and pyrithione is indeed synergistic. All challenges involved starting (challenge) concentrations of approximately 10^6 microorganisms per ml of test solution. After 72 hours in either 0.3% imidazolidinyl urea or 0.005% sodium
35 pyrithione, the concentration of microorganism was



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unchanged within experimental error, certainly less decrease than a factor of 10. The combination test solution would therefore be expected to have, after 72 hours, concentrations of microorganism either unchanged or at most decreased by a factor of 20. Yet the mixture of imidazolidinyl urea and sodium pyrithione, in fact, reduced the concentration of microorganism from 10^6 to 0 - a factor of 1,000,000.

The synergistic activity of the composition of the invention makes it a highly attractive preservative for a wide variety of products which are susceptible to contamination by microorganisms.

The composition of the invention is particularly attractive for use in cosmetic products. It is readily incorporated in aqueous-based products, emulsions and solid formulations. Moreover, because of its synergistic activity, the composition is effective in applications where the individual components are by themselves ineffective. Typical cosmetic products effectively preserved by the composition of the invention are creams, lotions, shampoos, hair conditioners, eyeliners, and other eye make-up products.

In addition to cosmetics, the composition of the invention may be used to preserve almost any substance which is susceptible to microbial contamination including foodstuffs and pharmaceutical formulations. While effective amounts will vary depending upon the product being preserved, generally the amount of the composition incorporated into a product will not exceed 1.0% by weight. In this amount, the pyrithione component(s) will generally be present in an amount from about 0.025 to 0.1%, the remainder of the composition being imidazolidinyl urea.

The invention, therefore, also relates to a method of preserving products susceptible to microbial



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contamination by incorporating therein an effective amount of the composition of the invention, and the products so preserved.

While the invention has now been described
5 in terms of certain preferred embodiments, 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
10 limited solely by the scope of the following claims.



CLAIMS:

1. A composition of matter comprising a major part of imidazolidinyl urea and a minor part of pyrithione and/or one or more derivatives of pyrithione.
- 5 2. The composition of claim 1, wherein said derivatives of pyrithione are selected from the group consisting of alkali metal salts of pyrithione, heavy metal salts of pyrithione and pyrithione disulfide.
- 10 3. The composition of claim 2, wherein said derivatives of pyrithione are sodium pyrithione and zinc pyrithione.
4. A product containing up to 1.0% by weight
15 of the composition of claim 1.
5. The product of claim 4, wherein said product is a cosmetic product.



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US83/01829

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC Int. Cl. ³ A01N 43/30; A01N 43/50; A01N 55/02 U.S. Cl. 424/245; 424/263; 424/273R		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	424/245; 424/263; 424/273R	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
Chemical Abstracts - subject 1909-1983 Lexis Computer Search		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A	US, A, 2,745,826, published 15 May 1956, Semenoff et al.	1-5
Y	US, A, 3,248,285, published 26 April 1966, Berke	1-5
Y	GB, A, 761,171, published 14 November 1956, Olin Mathieson Corporation	1-5
Y	N, Nelson et al., "Sodium and Zinc Omadine Antimicrobials as Cosmetic Preservatives", <u>Cosmetics and Toiletries</u> , 96(3): 87-90 1981.	1-5
Y	N, Rosen et al., "Preservation of Cosmetic Lotions with Imidazolidinyl Urea Plus Parabens", <u>J. Soc. Cosmet. Chem.</u> 28: 83-87 (1977).	1-5
Y	N, Rosen et al., "Modern Concepts of Cosmetic Preservation", <u>J. Soc. Cosmet. Chem.</u> 24: 663-675 (1973).	1-5
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²		Date of Mailing of this International Search Report ³
08 February 1984		14 FEB 1984
International Searching Authority ¹		Signature of Authorized Officer ²⁰
ISA/US		Allen Jay Robinson