What Exactly Are "Green" Antimicrobials?

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INTRODUCTION

Over the past two to three years there has been a noticeable global surge in biocide manufacturers' claims of "green" products and logos or trade names. This has resulted from pressure from various sources, including the consumer, environmental organizations, and government, as well as the natural evolution of technology and marketing. Unfortunately, many claims are far from what can be empirically designated "green," which prompts the question of what should be considered most important for a green claim, and where should we draw the line? In the context of the current article, antimicrobials include the following synonyms or descriptions: preservatives, biocides (bactericides, fungicides, and algaecides) and biostats used for the purpose of preserving the functional and chemical integrity of surface coatings in their wet or cured states—this does not include disinfectants, reclamation actives, (such as 2,2-dibromo-3-nitropropionamide) or their synonyms.

It would be reasonable to regard "green" antimicrobials as those with most of the following favorable attributes: (1) low mammalian toxicity (cytotoxicity), (2) low skin sensitization potential, (3) low eco-toxicity, (4) low bioaccumulation potential, (5) low emission potential during manufacture, application, or post-application, (6) no or low VOC content, as applicable, and (7) complete effectiveness against the relevant target organisms. There are a number of ways in which the human or environmental impact profile of a biocide can be improved, but not necessarily warranting a "green" claim or label. In order for a product to be truly "green," there should be very significant advantages over existing alternatives when considering the total or potential impact from cradle to grave. Merely producing an antimicrobial with a favorable human and environmental impact profile which still destroys natural resources during its manufacture or extraction can hardly be considered "green" overall. Furthermore, many "natural" alternatives to existing chemistries need

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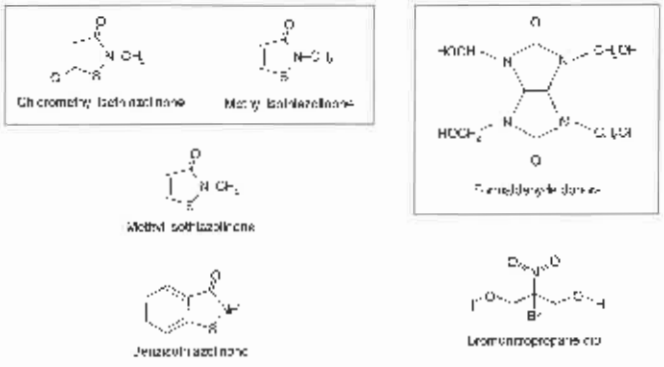
Figure 1—Most commonly used in-can antimicrobial active ingredients in surface coatings.



to be used at vastly higher addition levels, which often negates any benefits in application.

Biocides with relevance to surface coatings can be divided into "in-can" biocides, which serve to preserve the integrity of the coating during manufacture and in its packaging prior to application, and "dry-film" biocides, which serve to preserve the integrity of the coating post-application from fungal establishment (interior) or from fungal and algal establishment (exterior). Because these biocides have different functions, they need to be considered separately in reference to their "green" attributes. Also, it must be considered that any negative contributions of antimicrobials within the coating system will be relatively minor in terms of the entire coating volume; with dry-film biocides being more relevant in this respect. Therefore, emphasis on reducing any risks during distribution and use of the concentrated biocide is most common and relevant.

It is well known, within the existing global regulatory environment, that new or radically different antimicrobial chemistries are unlikely to be developed because of the enormous expense of development, toxicological testing, and registration (at various levels), resulting in a lengthy return-on-investment with little benefit to the manufacturer. Therefore, most manufacturers have concentrated on finding combinations of acceptable existing chemistries and altering any adverse attributes that the active ingredients might have, or removing (or reducing) organic solvents/co-solvents or carriers.

IN-CAN (WET-STATE) ANTIMICROBIALS

Over the past 20–30 years, many in-can antimicrobial active ingredients have fallen by the wayside, and have been replaced by ingredients with im-

Table 1—Attributes of Common In-Can Antimicrobial Active Ingredients (Part 1)

Molecule	Mammalian Toxicity in Application[a]	Sensitization Potential Threshold (ppm)[b]	Bioaccumulation Potential
CIT/MIT	Low	High 65	Low
MIT	Low	Low 15,500	Low
BIT	Low	Very Low 84,000	Low
HCHO-donors	Low	Low to High Unknown	Low
BNPD	Low	Low to Medium Unknown	Low

CIT/MIT: 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (ratio 3:1); MIT: 2-methyl-4-isothiazolin-3-one; BIT: 1,2-benzisothiazolin-3-one; HCHO-donors: various types of formaldehyde donors; BNPD: 2-bromo-2-nitropropane-1,3-diol.

(a) Taken into account practical use levels in ppm.

(b) LLNA (Local Lymph Node Assay): EC3 value. Concentration stimulating proliferation of lymph node cells by a factor of 3 (in vitro).

proved human and/or environmental impact potential; these, in themselves, previously being regarded as "greener" alternatives. Those currently used in surface coatings (and their relevant constituents) are given in *Figure* 1.

Some of the attributes with relevance to "green" claims for single-component in-can antimicrobial agents are given in *Tables* 1 and 2. None of the most common in-can biocides exhibit bioaccumulation potential, and their mammalian toxicities in consumer products would only be applicable upon ingestion (and will be low). Skin sensitization potential is, however, relevant and deserves special consideration. Consideration should also be given to long-term exposure and any carcinogenic associations, as has been implied for formaldehyde.

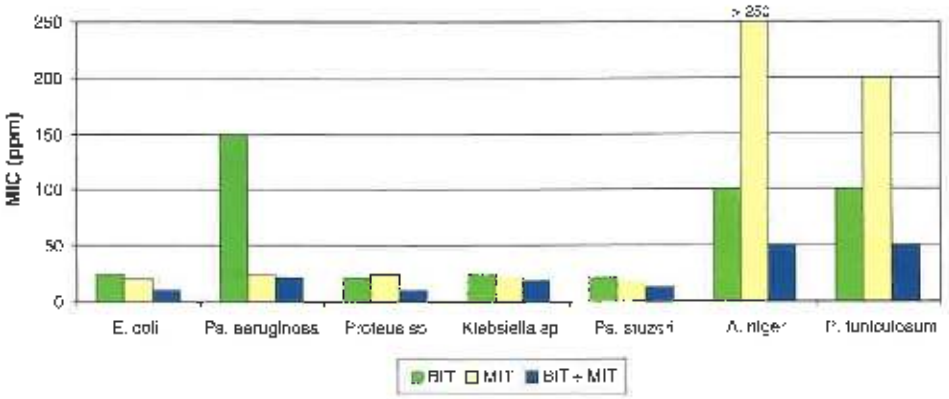
All of the compounds listed are readily soluble or miscible in water, with the exception of 1,2-benzisothiazolin-3-one (BIT), where the solubility will be influenced by (low) pH, and thus removal, dilution, and de-

Table 2—Attributes of Common In-Can Antimicrobial Active Ingredients (Part 2)

Molecule	VOC/Organic Solvent	Relative Long-term Stability	Relative Reactivity	Microbiological Activity Spectrum
CIT/MIT	No	Low	High	Complete
MIT	No	Very high	Low	Incomplete
BIT	Most	High	Low	Incomplete
HCHO-donors	Some[a]	Low-Medium	Medium–High	Incomplete
BNPD	Some[a]	Low	High	Incomplete

(a) Depends on type, or concentration.

Figure 2—Minimum inhibitory concentration assay (MIC) values of BIT, MIT, and a 1:1 ratio of a MIT/BIT combination product against various spoilage microorganisms.



contamination is relatively easy in all cases. In most surface coatings, 5-chloro-2-methyl-4-isothiazolin-3-one (CIT), 2-bromo-2-nitropropane-1,3-diol (BNPD), and some formaldehyde donors have lower relative stabilities, and thus their longevity in use is usually significantly shorter than MIT and BIT.

All single active ingredients listed in *Table* 2, with the exception of CIT/MIT, have incomplete microbiological activity spectra, or require relatively high amounts of active ingredient in order to provide complete prevention against microbiological contamination and spoilage. It is important, therefore, from a "green" perspective, to consider the total amount of biocide (in ppm) in the finished product to put any (negative) aspects into perspective.

MAKING EXISTING IN-CAN ANTIMICROBIALS 'GREENER'

There are a number of ways in which existing antimicrobials on the market can be "improved" from a human and/or environmental impact perspective. For example, BIT, once formulated only in glycol, is now available as a water-miscible alkali salt or as a water-dispersed micro-emulsion. The reduction in VOC of such a BIT-based biocide can, therefore, be very significant. Although this can be regarded as a step towards a "green" antimicrobial from an environmental perspective, the human impact potential remains unchanged—therefore, the "green" claim is, at best, only partial. Further steps can be made to make this BIT "greener." For example, combining an additional active ingredient with BIT (such as MIT) results in a combination product having up to a four-fold reduction in total active ingredient requirement (as a result of the synergy in antimicrobial activity). Examples of the synergies that result are given in *Figure* 2. The combination with another active ingredient represents step two in the "improvement" process; a water-based, synergistic blend (with lower human and environmental impact potential). A concomitant technical advantage would be the enhanced activity profile against many common spoilage organisms, including the most common spoilage organism group, the Pseudomonas and their variants (*Figure* 2).

Biocides based purely on CIT/MIT in an approximately 3:1 ratio have proven to be very effective, but have potential for skin-sensitization if used at high enough concentration, even though over the last 10 years the levels of sensitizing impurities have been vastly reduced. The relationships between "set-off" sensitization levels versus practical addition levels for CIT/MIT are given in *Figure* 3, and are compared with those of the MIT/BIT combination previously discussed. The advantage of the MIT/BIT combination over CIT/MIT in this regard is very clear, with MIT/BIT having a 16-fold difference versus a roughly two-fold difference for CIT/MIT.

There also have been more recent advancements in formaldehyde-donor chemistries, where newer variants with vastly lower free-formaldehyde levels have been developed, such as tetramethylol acetylene diurea (TMAD). This molecule emits significantly lower levels of free formaldehyde than its predecessors and can, therefore, be regarded as a "greener" alternative.

Figure 3—Set-off sensitization levels for MIT/BIT and MIT/CIT versus practical in-use concentration.

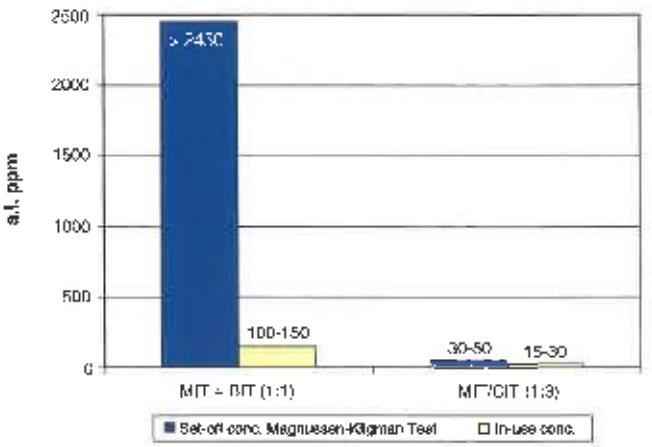


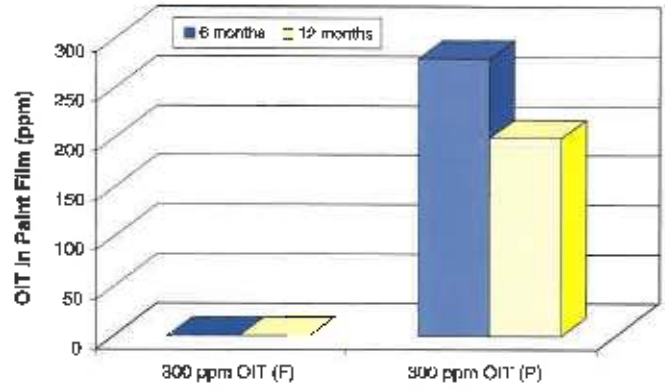
Table 3—Most Commonly Used Dry Film Fungicides and Algaecides in Surface Coatings

Molecule	Fungicidal Activity	Algaecidal Activity	Comment
OIT	+++	(+)	solubility[a] (leaches), sensitizer[c]
IPBC	+++	—	discoloration,[a] AOX, solubility[a] (leaches), sensitizer[a]
Carbendazim	+++	—	discoloration, activity spectrum gaps, EU labeling issues.
DCOIT	+++	(+)	AOX, low UV stability,[a] strong sensitizer,[a] pH limitations[a]
Chlorothalonil	+++	—	chalking, AOX, activity spectrum gaps
ZNP	+++	(+)	discoloration,[a] solubility[a] (pH-dependent), UV stability[a]
Diuron	—	+++	solubility[a] (leaches)
Triazines	—	[illegible]	severe EU labeling, eco-toxicity[a]

(a) Can be modified with "protection" technology.
AOX: absorbable organic halogens. OIT: 2-n-octyl-4-isothiazolin-3-one; IPBC: 3-iodopropynylbutylcarbamate; Carbendazim: Methyl 1H-(2-benzimidazolyl) carbamate; DCOIT: 4,5-dichloro-2-(n-octyl)-4-isothiazolin-3-one; Chlorothalonil: 2,4,5,6-tetrachloro-1,3-dicyanobenzene; ZNP: Zinc bis(2-thiolPyridine N oxide); Diuron: 3-(3,4-dichlorophenyl)-1,1 dimethylurea; Triazines: 2-tert-butylamino-4-ethylamino-6-methylthio-1,3,5-triazine and cyclopropyl-N-(1,1-dimethylethyl) 6-(methylthio)-1,3,5-triazine-2,4-diamine.

No "green" in can antimicrobial solution would be complete, however, without some input or effort on the part of the coatings manufacturer. It is one thing enabling combinations of various active ingredients to be used at lower addition levels because of synergy or additive effects, but we must not forget that changing a preservative system will usually require consideration from more than one perspective. It is important to consider the point of biocide addition during manufacture, that the replacement is suitable for the purpose and is compatible, and that a facility is checked for its microbiological condition. Merely substituting one biocide for another when problems occur usually is not the solution, since the underlying cause might still exist regardless of any idealistic "silver bullet" biocide being incorporated. Where biofilms or poorly managed wash water inventories exist, bacterial tolerances can be developed, resulting in spoilage post-manufacture regardless of the biocide being used. Requirements exceeding 750 ppm active ingredient for single-component biocides (e.g., formaldehyde donors and BIT) have been recorded in our laboratories, which is significantly higher than their normal recommended use concentrations.

Figure 4—Reduction of solubility expressed as retention of free (F) and protected (P) OIT within a paint film following 6 and 12 months' exterior exposure in Europe.



DRY FILM ANTIMICROBIALS

A similar evolution of elimination and improvements has occurred with dry film biocides. The most

Figure 5– (a) Retention of protected zinc pyrithione [ZnP(P)] versus free zinc pyrithione [ZnP(F)] in four different coatings following two and three years' exterior exposure and (b) retention of free diuron [Diuron (F)] and protected diuron [Diuron (P)] following two days leaching for four different coatings.

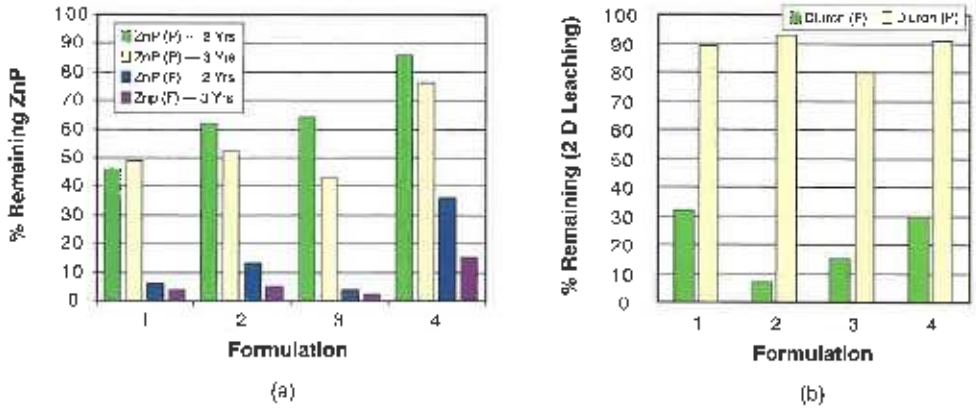
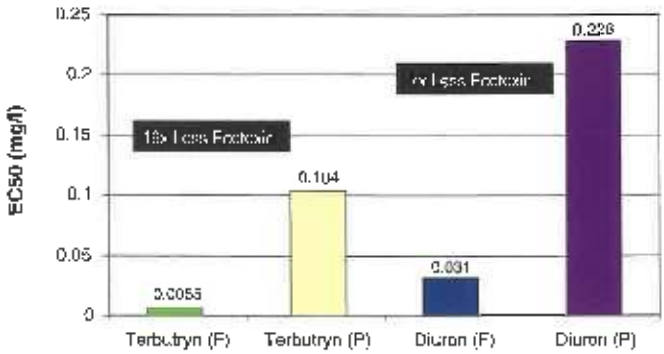


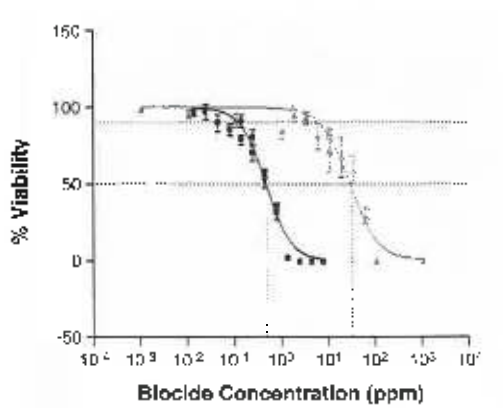
Figure 6—Reduction in ecotoxicity (Algal EC_{50}) of protected (P) versus free (F) terbutryn and diuron algaecides. A higher concentration signifies lower ecotoxicity.



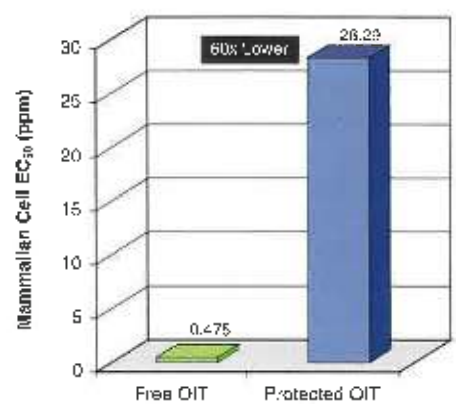
commonly used fungicides and algaecides in surface coatings are given in *Table* 3.

Dry film biocides are typically used at a higher addition levels (in ppm) than in-can biocides, thus enhancing any potential impact. As is evident from *Table* 3, no single active ingredient has the versatility to provide universal anti-fungal and anti-algal protection at practical addition levels, and all of the active ingredients listed have some property which has some environmental, human exposure, or technological/functional limitation. However, as was the case for in-can biocides, any functional limitation can be resolved by combining more than one molecule together, which may have synergistic or additive advantages. Also, it is generally understood that many adverse effects of single active ingredients are concentration-dependent, and could be resolved by combining multiple actives.

Figure 7—(a) Reduction in cytotoxicity (mammalian) of free (black line/dot) and protected (gray line/triangle) OIT using the 3T3 neutral red uptake assay (*in-vitro*). (b) Graphic representation showing the significance of the reduction in mammalian cytotoxicity of protected OIT.



(a)



(b)

Figure 8—Reduction in emission of protected OIT (P) versus free OIT (F) in two tests, following 24 hr and six weeks' post application in a chamber at 40°C.

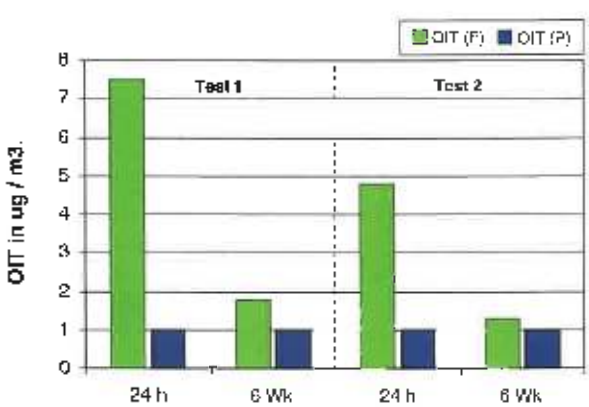
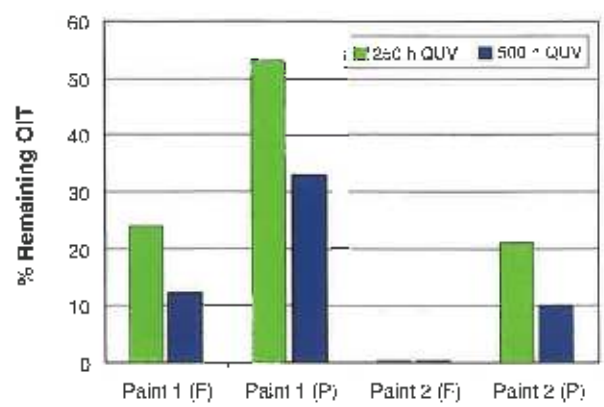


Figure 9—Improvement in UV stability of protected OIT (P) versus free OIT (F) in two paints following exposure to 250 and 500 hr QUV.



MAKING EXISTING DRY-FILM ANTIMICROBIALS "GREENER"

One of the general properties required by a dry-film biocide (particularly for exterior application) is low-water solubility to prevent the biocide from being leached out of the film too quickly. As a result, it comes as no surprise that most dry-film biocide active ingredients were originally distributed in a non-polar solvent or glycol. Over the years, "greener" versions of these active ingredients have been made available as stable water-based dispersions or micro-emulsions. Although these could be regarded as improvements, they remain far from "green" since most issues lie with the active ingredients and not their carriers.

More recently, the development of "protection" technologies for active ingredients (including various forms of "encapsulation" and other "retardation" techniques) have enabled the next generation of "greener" dry film antimicrobials to be introduced. Apart from the obvious advantages of protecting against exposure to a high concentration of the active ingredient all at once, there are often technical advantages associated with such developments. In fact, special protection technologies can improve all but one negative aspect of the molecules listed in *Table* 3—that being the biocidal activity spectrum. However, as previously mentioned, intelligent design of combination antimicrobials can easily eliminate that aspect. The release mechanisms of protected active ingredients from their repositories may be variable, depending on the technologies employed, and the results in practice may differ. Examples of advantages of various protected actives are given here:

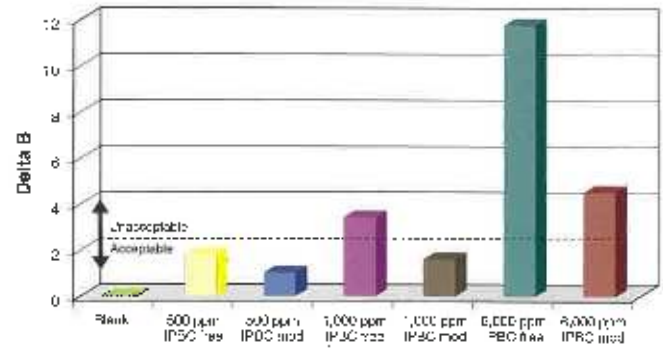
(a) A reduction in solubility usually results, extending life-expectancy in the coating, and in some cases enabling a significant reduction in active ingredient requirement (*Figures* 4 and 5).

(b) A reduction in environmental impact, with lower immediate levels of active ingredient being available at any one time (*Figure* 6).

(c) Lower mammalian toxicity. *Figure* 7 shows the dramatic reduction in cytotoxicity of protected OIT versus free OIT (up to 60X). Another advantage would be the reduction in potential exposure during or post application of the coating, which is particularly relevant for interior coatings (*Figure* 8).

(d) Improvement in UV stability is a technical benefit of some types of protection technology, particularly with relevance to DCOIT and OIT (*Figure* 9), as is the reduction in discoloration potential for active ingredients such as zinc pyrithione and IPBC (*Figure* 10). This further obviates or decreases the need for additional UV stabilizers or oxide salts to lessen such effects.

Figure 10—Reduction in discoloration (Delta B value) when using protected IPBC (mod) versus free IPBC (free).



Other benefits of protected actives include lower odor-forming potential, lesser effect on the coating system viscosity, and reduced adverse film effects, such as chalking.

No attempts to improve the impact profile of any active ingredient will be acceptable, nor complete, unless proof can be furnished that the efficacy of the modified antimicrobial(s) meets the requirements of their intended function and many trials have been conducted demonstrating their fitness for purpose. Up until now, the benefits of removing unwanted compounds from antimicrobial formulations and the enormous benefits of reducing exposure by combining existing active ingredients, as well as modifying or protecting them (by encapsulation or similar means) to minimize any of their negative potential exposure attributes, has moved formulation of antimicrobials to the next, "greener" level. Not only has this provided the intended benefits, but has given many consequential technical benefits, as previously shown. While all this can be considered deliberate movement in a green direction, what is regarded as green today might not be regarded as green tomorrow. However, it can be argued that huge strides have been made as part of normal product development or progression, and increased awareness of relevant attributes (as discussed) will enable readers coming across green claims to distinguish for themselves how "green" the development really is, and what is just "green advertising."

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