ANTIBACTERIAL RESISTANCE

INTRODUCTION

On January 22, 1997, a joint meeting of two FDA Advisory Committees agreed that the evidence to date indicated that topical antimicrobial wash products do not contribute to microbial resistance. They further suggested that on-going surveillance for the possible development of resistance to these agents is prudent.¹

This briefing document as well as our August 27, 2003 submission supports the facts that

- there is no evidence of decreased susceptibility of bacteria to antimicrobial agents under use conditions or in the environment;
- there are reviews by other institutions of the available data that conclude that decreased susceptibility, i.e., resistance, is not a problem under current use conditions; and
- there are existing on-going programs that are available to monitor the possible emergence of resistance to topical antimicrobial agents.

SURVEILLANCE STUDIES

A number of surveillance studies have been conducted looking for organisms with decreased susceptibility to antimicrobial agents in natural environments. There was no evidence of shifts in populations or development of resistance to the antimicrobial agents in any of these studies. Nor was there any evidence of a correlation of resistance between antimicrobial-tolerant strains and antibiotic resistant strains.

A. Factory Survey

Lear et al. (2002) examined over 100 isolates from triclosan and para-chloro-meta-xylenol (PCMX) manufacturing sites. The minimum inhibitory concentrations (MICs) of these isolates were compared with equivalent culture collection strains. They concluded that there was no evidence that the residual levels of biocides in the factory environment had led to changes in susceptibility. This study looked at

¹ Transcript of the joint Nonprescription Drugs Advisory Committee and Anti-Infective Drugs Advisory Committee on January 22, 1997.
sites where there was the greatest expectation of finding resistant strains, and none was found. Based on this finding, it would be unexpected to find resistant strains where exposure to these biocides is more casual, i.e., in homes. In reviewing this study Gilbert and McBain (2002) concluded that any changes seen in the flora was due to clonal expansion of pre-existing resistant but less competitive species.

B. Home Surveys

Marshall et al. (2003) compared the incidence of bacteria, including antibiotic resistant bacteria, in the homes of users and non-users of antibacterial agents. The authors concluded that high frequencies of antibiotic-resistant bacteria occurred in the home environment of both groups. However, there were no significant differences in the overall titers of bacteria, potential pathogens, or frequencies of antibiotic resistance in a single-time analysis of homes whether using or not using antibacterial-containing products.

Cole et al. (2003) sampled 60 homes split evenly between users and non-users of biocides including triclosan. There was no significant difference found in the level of antibiotic resistance between the users and non-users. The results also showed no evidence of cross-resistance between antibiotics and biocides in either the users or non-users. The non-user group did, however, have a significantly greater number of potentially pathogenic organisms present.

Aiello et al. (2004) examined the triclosan and antibiotic susceptibility of staphylococci and Gram-negative bacteria isolated from the hands of individuals in a community setting. Triclosan-containing or non-antimicrobial soaps were provided to the study population for one year. There was no statistically significant association between triclosan MICs and susceptibility to the antibiotics tested. This could indicate that such a correlation does not exist.

McBain et al. (2003b) examined the triclosan and antibiotic susceptibility profiles of bacteria in drains where there was constant exposure to dilute triclosan-containing products over a three month period. No shifts in the floral composition were seen, nor were there any significant changes in triclosan or antibiotic susceptibility.

Aiello et al. (2005) examined whether household use of antibacterial cleaning and hygiene products is an emerging risk factor for the carriage of antimicrobial drug-resistant bacteria on the hands of household members. Over two hundred households were randomized to the use of antibacterial or non-antibacterial cleaning and hygiene products for one (1) year, including the use of a handwashing soap containing 0.2% triclosan. The authors conclude that the use of antibacterial products did not lead to a significant increase in antimicrobial drug resistance nor was there an effect on bacterial susceptibility to triclosan.
C. Clinical Isolates

Al-Doori et al. (2003) surveyed the methicillin-resistant Staphylococcus aureus (MRSA) isolates in the Scottish Reference Library. The triclosan MIC\textsubscript{50} was 0.03 mg/L, and the triclosan MIC\textsubscript{90} was 0.06 mg/L within a range of <0.015 to 4 mg/L. The two dominant UK epidemic strains were both susceptible to triclosan. The study did not support the contention that the wide-spread use of triclosan in various products will select for resistance in MRSA.

Randall et al. (2003) surveyed 443 campylobacter species from humans and animals for multiple drug resistance to antibiotics and biocides. The rate of isolation of multidrug resistant campylobacter (3.3% for C. jejuni and 3.8% for C. coli) was lower than expected. The cross-resistance of these strains was also lower than expected. Some strains that were less susceptible to triclosan were significantly more resistant to six antibiotics suggesting a different mechanism may play a role.

Lambert (2004) analyzed MIC data from a study of 256 clinical isolates of Staphylococcus aureus [169 methicillin-sensitive Staphylococcus aureus (MSSA) and 87 methicillin-resistant Staphylococcus aureus (MRSA)] and 111 clinical isolates of Pseudomonas aeruginosa against eight antimicrobial biocides and several clinically relevant antibiotics. Between 1989 and 2000, a subpopulation of MRSA had acquired a higher resistance to biocides, but this had not altered the antibiotic susceptibility of that group. These strains were surveyed for their susceptibility to a wider group of biocides and antibiotics. Numerous correlations were shown between the MICs of antibiotics and biocides. However, many of these correlations were negative, i.e., an increase in MIC of a particular biocide was correlated with a decrease in the mean MIC of a particular antibiotic. Advanced statistical investigation using the method of principal component analysis grouped, in general, the antibiotics and the biocides separately. The groupings appeared to reflect the mode of action of the antimicrobials. In many cases the groupings showed little interaction, suggesting that little cross-resistance exists between antibiotics and biocides.

Schmid and Kaplan (2004) surveyed clinical isolates of S. aureus and S. epidermidis reconfirming the existing literature that S. epidermidis is more heterogenic as a species and is generally less sensitive to triclosan. The S. aureus and S. epidermidis strains surveyed were susceptible to triclosan.

Fan et al. (2002) studied the inherent variation in MIC of clinical isolates of S. aureus. All of the isolates studied were within the MIC bounds of what would be considered susceptible. These levels are also well within the normal range of susceptibility of S. aureus to triclosan. Strains with higher MICs were shown to have elevated levels of ACP reductase (Fab I enzyme) as compared to strains
with lower MICs. This study shows one mechanism whereby there is natural variation in the MICs of varying strains of *S. aureus*.

In some cases a decreased susceptibility to an antimicrobial is linked to a decrease in susceptibility to an antibiotic. However, there are also examples where decreased susceptibility to an antimicrobial can increase the susceptibility to an antibiotic. In other cases there is no such correlation proven, *e.g.*, populations of MRSA are as equally sensitive to triclosan as are MSSA.

**EXPERT REVIEWS ON RESISTANCE**

A number of expert reviews by Russell (2003; 2004) and Gilbert (*Gilbert et al.*, 2002; Gilbert and McBain, 2002) have concluded that while cross-resistance to biocides and antibiotics can be demonstrated in the laboratory using pure cultures, it does not necessarily equate to the development of such resistance in the natural or clinical environment where complex, multispecies biofilms predominate. No convincing evidence has been found to support the contention that triclosan usage has resulted in the clinical development of antibiotic-resistant Gram-negative bacteria, antibiotic-resistant cocci or isoniazid-resistant *M. tuberculosis*.

Goodfellow *et al.* (2003) reviewed the safety and efficacy of triclosan and concluded that the use of triclosan in cosmetic and over-the-counter drug products was safe and not expected to select for antimicrobial resistant bacteria. Furthermore, Kampf and Kramer (2004) reviewed the epidemiologic background of hand hygiene and evaluated the most important agents for scrubs and rubs. The authors concluded that triclosan has a low potential for acquired bacterial resistance. They also state that no acquired resistance has been reported to date for ethanol, isopropanol, or n-propanol. This is consistent with the biocidal action of alcohol, *i.e.*, cell membrane disruption and protein denaturation and the fact that an extensive literature search failed to reveal any citation of acquired microbial resistance to alcohol antisepsis.

Finally the European Commission’s Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP, 2002) reviewed the safety of triclosan and concluded that triclosan does not pose a risk to humans or to the environment by inducing or transmitting antibacterial resistance under current conditions of use (SCCNFP, 2002).

**MONITORING PROGRAMS**

At the present, there are existing programs within the U.S. that can be used to track antimicrobial resistance. These include the National Nosocomial Infections Surveillance (NNIS) program and the Interagency Task Force on Antimicrobial Resistance (NNIS, 2004; CDC, 2004). The NNIS is a joint program that has been
in place since 1970 between the Centers for Disease Control and Prevention (CDC) and 315 acute care hospitals. This program can track trends in antimicrobial resistance. A more recent program is the Interagency Task Force on Antimicrobial Resistance that is a joint program between the CDC, the National Institutes of Health, and the Food and Drug Administration together with other affiliated agencies and departments. This task force is developing and implementing a coordinated national plan for the surveillance of antimicrobial resistance (CDC, 2004).

CONCLUSION

Antibiotic resistant and antibiotic sensitive bacteria are equally sensitive to the in-use concentration of antimicrobials. There is no evidence in real world situations such as the home, food manufacturing, and industrial environments, outside the laboratory that antimicrobials can select for antibiotic resistant bacteria. Existing national programs which currently monitor antibiotic resistance could be modified to monitor bacterial susceptibility to antiseptic active ingredients.
REFERENCES


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