KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
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April 27, 2006

Public Information and Records Integrity Branch (PIRIB) (7502C)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
1200 Pennsylvania Ave., NW.
Washington, DC 20460-0001

Attention: Docket ID number EPA-HQ-OPP-2006-0234

Dear Sir or Madam,

On behalf of Keep Antibiotics Working (KAW), a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups, I write to urge you to deny the request from the Michigan Department of Agriculture for a specific exemption to use the pesticide gentamicin to control streptomycin-resistance fire blight.

KAW believes that the pesticide use of this highly important medical drug presents an avoidable and significant risk to public health. Indeed, we question whether highly important human drugs like gentamicin should ever be broadcast sprayed as pesticides, due to concerns about their contribution to antimicrobial resistance, and resultant threats to human health.

Gentamicin is highly important for the treatment of serious infections in humans.

When an application for the registration of gentamicin as a pesticide was made in 1994, KAW member group the Union of Concerned Scientists (UCS) opposed the registration on public health grounds (KAW Attachment 2: UCS Letter), because of the risk of antimicrobial resistance. At the same time, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the American Society for Microbiology all opposed the registration on human health grounds as well (reported in McManus, 2002). CDC (KAW Attachment 3: CDC Letter) noted at that time that gentamicin continues to be an important drug for treating sepsis in adults and is particularly important for treating neonatal sepsis. CDC also noted that the environmental use of this pesticide would increase the risk of resistance developing, because bacteria in sprayed orchards would be exposed to a concentration gradient of the pesticide. The concerns expressed by these commentators on the application for gentamicin registration are still relevant.

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The World Health Organization designated gentamicin a critically important drug for human medicine (WHO, 2005). FDA considers gentamicin and other aminoglycosides as highly important for human medicine, because of their importance in treating enteroccocal endocarditis and other serious infections (FDA, 2003).

Gentamicin is particularly important for the treatment of neonatal sepsis. While cephalosporins have increasingly been used as an alternative, recent research has shown that this may be misguided in the absence of specific information on gentamicin resistance. In a large study examining the outcomes of patients in a neonatal intensive care unit Clark et al. (2006) found lower mortality in patients that received gentamicin concurrently with ampicillin than in patients receiving cefotaxime with ampicillin.

Despite problems with nephrotoxicity and ototoxicity, Aminoglycosides have distinct properties that make them useful including "concentration-dependent bactericidal activity, postantibiotic effect, relatively predictable pharmacokinetics, and synergism with other antibiotics" (Vakulenko and Mobashery, 2003).

Aminoglycosides are important for treating a variety of serious illnesses. They are used to treat serious infections caused by aerobic gram-negative infections including Enterobacteriaceae and Pseudomonas aeruginosa usually in combination with other drugs (Vakulenko and Mobashery, 2003). Escherichia coli, a member of the Enterobacteriaceae family, has been detected on apples while apple products have been associated with illness caused by E. coli (Lang et al, 1999). Pseudomonas aeruginosa is a common cause of serious nosocomial infections. While the connection between resistant fruit pathogens and nosocomial infection may seem remote, there is evidence that genes conferring high level beta-lactam resistance in hospital Pseudomonas infections originated in the fruit pathogen Xanthamonas citri (Jones, 2005).

Aminoglycosides are also important for treating enteroccocal infections including enteroccocal meningitis (Tunkel et al., 2004) and infective endocarditis (Baddour et al., 2005). Enterococci are readily found on apples even after washing (Lang et al., 1999). KAW believes the use of gentamicin as a pesticide for fruit in response to streptomycin resistance in the fruit pathogen is particularly misguided because gentamicin is used to treat human enteroccocal infections that have become resistant to streptomycin (Baddour et al., 2005). Enterococci resistant to both streptomycin and gentamicin would be more difficult to treat than bacteria resistant to either one singly.

Gentamicin and streptomycin are the treatments of choice for tularemia (Maurin and Raoult, 2001). Because there is not cross resistance between streptomycin and gentamicin, one may be substituted for the other when resistance is present. Using gentamicin in an orchard where streptomycin resistance is already high may lead to tularemia that is difficult to treat. There are alternatives to aminoglycosides for tularemia treatment, but these have higher relapse rates (Hassoun et al., 2006). Tularemia can be found everywhere in the state of Michigan and infects animals common in orchards such as rabbits (Michigan DNR, 2006). The exposure of infected animals to low levels of gentamicin, which is likely when the drug is sprayed on fruit

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trees, will increase the risk of gentamicin resistance in the bacteria that cause tularemia. The likelihood that this will occur is increased because spraying occurs in the spring, the same period when the disease is most prevelant.

The risk that gentamicin when used as a pesticide will create a public health hazard through the selection of resistant bacteria has not been evaluated by the EPA.

KAW believes that information on the public health risks of the pesticide use of gentamicin was sufficient to deny the application for registration and is sufficient to deny this request for a specific exemption. If the EPA does not believe that this information is sufficient to deny the request for an emergency exemption, then EPA should complete an assessment of the risk before approving the exemption. EPA recently published and asked for comments on assessments of the risks of antimicrobial resistance from the pesticide use of streptomycin (EPA Docket ID Number EPA-HQ-OPP-2005-0493) and oxytetracycline (EPA Docket ID Number EPA-HQ-OPP-2005-0492). The EPA modeled these risk assessments on the FDA's Guidance for Industry 152. Both found either a medium or high risk for creating adverse human health impacts. This approach, if applied to the risk assessment of the human health hazard from the pesticide use of gentamicin, would likely lead to the same result. Resistance to gentamicin like other aminoglycosides is commonly carried on mobile elements that are readily transferred between bacteria. Although there are no reports of gentamicin resistance in fruit pathogens in Michigan, this says nothing about the risk of using this highly important antibiotic as a pesticide; rather, it only reflects the absence of use of this unregistered pesticide. Without a thorough assessment of the risks of antimicrobial resistance developing from this proposed emergency use of gentamicin, it is inappropriate to accept the request.

Because streptomycin-resistant fire blight occurs every year in Michigan, it is inappropriate to consider this situation an emergency.

According to the Federal Code (40CFR166.3), an emergency condition is a "non-routine situation." Streptomycin resistance in the fire blight pathogen is a routine condition in Michigan and should not be considered an emergency. This is particularly true given that the claimed emergency occurred because fruit growers decided to grow susceptible fruit varieties on susceptible root stock planted at higher densities than what has been traditionally followed in Michigan (Longstroth, 2002). An alternative approach would be to plant resistant varieties at healthy stocking densities and market the fruit as antibiotic free.

Conclusion:
KAW urges EPA to deny the request for a specific exemption by the Michigan Department of Agriculture to use the unregistered pesticide gentamicin to control streptomycin-resistant fire blight. KAW believes that the pesticide use of gentamicin is likely to compromise the usefulness of this highly important medicine in treating serious human illness.

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Sincerely,

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