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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-2005-0493

Dear Sir or Madam,

Keep Antibiotics Working (KAW) appreciates this opportunity to submit comments on the Environmental Protection Agency's risk assessment for the pesticide streptomycin. Antimicrobial resistance is a growing human health problem and all uses of antimicrobials must be appropriately managed to limit the spread of resistance generally, but also specifically for streptomycin, which has important human uses such as for treating resistant tuberculosis, tularemia, plague, endocarditis and bacteremia. KAW commends the EPA for acknowledging the importance of antimicrobial resistance in the safety assessment of this group of pesticides. KAW encourages the EPA to quickly implement steps to address the risk of adverse human health impacts as determined by Tolerance Reregistration Eligibility Decision Document (TRED) risk assessment.

Keep Antibiotics Working (www.KeepAntibioticsWorking.com) is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in food animals. To ensure the continued effectiveness of antibiotics important for treating sick people and animals, KAW advocates for a responsible approach to antibiotic use in agriculture. While the primary focus of KAW is upon antimicrobial use in food animals, we believe that it is important that all agricultural uses of antibiotics be managed to limit the public health risk.

KAW, in principle, believes that antibiotics that are important for treatment of human diseases should not be used as pesticides, because this will inevitably lead to resistance which poses a threat to public health. The use of antibiotics as spray pesticides is particularly problematic as this will result in bacteria in the orchard environment being exposed to low levels of the antibiotic which presents a greater risk of resistance selection. This was the position of the Centers for Disease Control (CDC) in 1998, when they opposed the registration of gentamicin as pesticide (CDC, 1998). At the same time, the CDC also recommended the elimination of the other environmental uses of medically important antibiotics including streptomycin.

To the extent that risk assessment is necessary, KAW supports the EPA basing its risk assessment on the Food and Drug Administration's (FDA) Guidance for Industry #152 (Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their

Microbiological Effects on Bacteria of Human Health Concern.). In addition to minimizing the duplication of effort, the EPA by applying an approach consistent with the FDA in evaluating the agricultural antimicrobials under EPA's regulatory authority increases public confidence in the government's risk assessment activities.

While KAW supports the EPA using the approach recommended in Guidance #152, we are concerned that EPA is not proposing risk management steps consistent with the Guidance. The EPA has determined, as described in the Health Effects Division Chapter (HED) of the streptomycin TRED, that the pesticide use of streptomycin presents a medium level of risk of adversely impacting human health for occupational application and a high level for residential application. KAW believes for reasons described below that the appropriate level of risk should be high for any use of streptomycin as a pesticide. For this level of risk from an agricultural antibiotic, FDA recommends the following restrictions: marketing status limitations, limitations on extent of use, and post approval monitoring for resistance. Extra-label use restriction and advisory committee review should also be considered.

KAW recommends that EPA require management steps consistent with those recommended for high risk drugs under Guidance #152. Streptomycin for fire blight control is typically used prophylactically and broadly, across the entire farm and in many cases across the region. This type of application, however, is inconsistent with the extent of use limitations recommended by Guidance 152 for antibiotics with a high human health risk. Guidance #152 recommends that antibiotics at this risk level be restricted to individual animal treatment, not farm-wide treatment, for less than 21 days. Streptomycin as a pesticide is currently used for farm wide disease control for more than 21 days.

KAW therefore recommends that streptomycin as a pesticide be used only to treat individual infected plants if at all and that treatment be limited to less than 21 days to be consistent with FDA risk management options. This would mean that the control of fire blight is not an appropriate use of this antibiotic.

Not only is the use of streptomycin an unreliable treatment for fire blight because of the presence of resistance, there also are other effective methods for controlling fire blight that avoid the public health concerns raised by use of a medically important class of antibiotics as pesticides. Significantly, the use of antibiotics greatly increased in orchards because during the 1990s fruit growers began planting trees closer together and began planting susceptible varieties of fruit trees during the 1990s (Steiner, 1998). Even with antibiotic controls a combination of predictable weather conditions and unwise farm management decision led to widespread damage from this disease in Michigan in the year 2000 (Longstroth, 2002). Because of the inevitable development of resistance, antibiotics should not be considered a sustainable solution to this problem. The efficacy of this pesticide has already been compromised by resistance in regions where weather conditions increase the risk of this plant disease.

If streptomycin is to be used as a pesticide only for individual treatment of infected plants, the Guidances other recommended risk management steps should also be followed. Specifically, streptomycin be labeled a restricted use product to meet the recommended marketing restrictions and antimicrobial resistance monitoring should be required with isolates submitted into the National Antimicrobial Resistance Monitoring System.

While KAW believes that the application of Guidance #152 to the pesticide use of streptomycin as described in the HED is the appropriate approach to risk assessment given the limited data that is now available, the risk assessment itself can and should be strengthened.

KAW's greatest concern is that EPA in examining the antimicrobial risk of the pesticide use of streptomycin is only considering the foodborne exposure pathway. While this is the approach taken by the FDA, FDA has argued that it does not consider other exposure pathways because they are outside FDA's regulatory scope and has stated that non-food pathways are instead within the scope of the US EPA (FDA, 2004). KAW believes EPA should take a more active role in assessing the risk from all agricultural uses of antimicrobials given that FDA views doing so as beyond the scope of FDA's regulatory authority.

If EPA fails to consider potential environmental pathways in its assessment of risk, an important pathway for the transfer of resistance will be left unexamined. This is particularly true because the environmental use of streptomycin is likely to expose bacteria on other plants and animals present in orchards, in addition to the targeted trees. If environmental pathways are included in the exposure assessment, it is likely that the outcome would be high as opposed to medium. Streptomycin is considered the first line treatment choice for both tularemia and plague. Both these diseases are carried by animals that are common in orchards and which are likely to be exposed to the pesticide spray.

While there are other treatment options available, streptomycin is the preferred treatment for tularemia and plague. The HED argues that there are alternative drugs for the treatment of both these diseases. While this is correct, other drugs may have less efficacy, higher cost, and greater likelihood of causing allergic reactions. Streptomycin will also be the empirical treatment until resistance testing is completed. For resistant pathogens this increases the risk of complications and likely will extend the duration of the illness. The availability of alternatives does not mean that harm has not been done when resistance to the treatment of choice occurs.

Streptomycin is also used to treat resistant enterococcal endocarditis. Enterococci, the infective agents in endocarditis, have been detected on apples (Lang et al., 1999). The HED emphasizes the importance of streptomycin for treating resistant tuberculosis but the other indications are also important.

This risk for environmental exposure is probably higher in occupational application than in residential because of the large area over which the antibiotics will be applied. Given that streptomycin resistance persists between years, it is difficult to see how a 12-hour reentry interval and protective clothing reduce the exposure to resistant bacteria to any extent. For this reason, KAW believes that both the residential and occupational exposure assessments should be high. Ignoring environmental pathways in assessing the risk from Streptomycin and assuming that streptomycin is only important in the treatment of tuberculosis is highly likely to underestimate risk.

KAW agrees with EPA that the information of current levels of resistance in the plant pathogens warrants a high ranking in the release assessment. KAW does not believe that this risk is greater in residential as opposed to commercial application for the reasons described above in our comments on the exposure assessment. The EPA also states that homeowners are more likely to dispose unused product improperly and are more likely to re-apply the product too often, without providing any sources to support this assertion. Without any evidence to support this claim EPA should assume that both homeowners and commercial applicators are equally likely to misuse the product. Given the current levels of resistance in orchards, it unclear that fruit growers are properly handling these products.

The HED suggests that monitoring resistance for bacteria from fruits that are commonly treated with antibiotic pesticides would be helpful in refining the risk assessment. While this would be useful, combining this with data on antibiotic use would be better. Ideally orchards where streptomycin is used and fruit from treated orchards should be monitored for resistance. Data from treated orchards should then be compared with data from regions where streptomycin has not been used. Data on resistance prevalence in fruit that is not combined with pesticide use data will be difficult to interpret.

KAW agrees that additional usage data on all agricultural antimicrobials would be helpful for assessing the risks and for identifying resistance problems as they arise. The FDA has had a proposed data rule under evaluation since at least 2002, but has failed to make it public despite data collection being a priority action item in the Public Health Action Plan to Combat Antimicrobial Resistance (Interagency Task Force on Antimicrobial Resistance, 2001). KAW recommends that EPA request that FDA begin collecting usage data on the agricultural antimicrobials regulated by the FDA.

In conclusion, KAW commends EPA for considering the human health impact of antimicrobial resistance in its evaluation of the safety of the pesticide use of streptomycin. KAW also supports the EPA using a methodology consistent with the FDA's evaluation of the risks of other agricultural uses of antimicrobials. KAW strongly encourages EPA to apply risk management steps consistent with the FDA approach. In particular, KAW believes that the prophylactic use of streptomycin to treat whole orchards is an inappropriate use of this highly important antibiotic and that this use is inconsistent with risk management options that are appropriate for a pesticide determined to be of high risk for creating an adverse human health impact. KAW believes that the exposure assessment and consequently the overall assessment should be high for both

residential and commercial applicators. KAW requests that EPA take action to limit the use of this drug to appropriate uses given this high risk to public health.

References

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