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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–2005–0492

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 oxytetracycline. 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 tetracyclines, which have important human uses such as for treating Lyme's disease, respiratory tract infections, and as an alternative antibiotic for people allergic to penicillins. 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 medium risk of adverse human health impacts as determined by Tolerance Reregistration Eligibility Decision Document (TRED).

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 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 oxytetracycline.

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 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 oxytetracycline TRED, that the pesticide use of oxytetracycline presents a medium level of risk of adversely impacting human health. 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 medium risk drugs under Guidance #152. Because oxytetracycline for fire blight control needs to be applied before infection occurs, it typically would be 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 medium human health risk.

Guidance #152 not only recommends that antibiotics at this risk level be restricted to select pens, not farm-wide treatment, but also prescribes the duration of application for less than 21 days. Oxytetracycline as a pesticide is currently used for farm wide disease control for more than 21 days.

KAW therefore recommends that oxytetracycline as a pesticide be used only to treat individual infected plants 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 oxytetracycline an unreliable treatment for fire blight, 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 (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.

In addition to complying with the provisions of Guidance #152 by using oxytetracycline as a pesticide only for individual treatment of infected plants, the Guidance's other recommended risk management steps should also be followed. Specifically,

oxytetracycline should 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 oxytetracycline as described in the HED is the appropriate approach to risk assessment given the limited data 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 oxytetracycline 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 noted that non-food pathways are instead within the scope of the US EPA (FDA, 2004).

If EPA fails to consider potential environmental pathways in its assessment of risk, this leaves an important pathway for the transfer of resistance unexamined. This is particularly true because the environmental use of oxytetracycline 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. 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.

KAW is also concerned that the release assessment described in the HED used the lack of information on the extent of resistance present in orchards as the basis for a medium release assessment. As is clearly stated in the box on page 13 of Guidance #152, when there is a gap in the data to evaluate a factor to be considered in the release assessment, the most conservative value should be assumed. Combining this lack of information about the extent of resistance in orchards with the information confirming the presence of resistance in orchards and the information that tetracycline resistance is carried on mobile elements, KAW believes that an appropriate release estimate would be high. A high assessment is also supported by the increased likelihood of resistance selection linked to the concentration gradient. While this would not change the overall risk assessment of medium, KAW believes that it is inappropriate to use lack of information as a factor mitigating risk and allowing it in this case would set a dangerous precedent for other EPA risk assessment activity.

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 oxytetracycline is used and fruit from treated orchards should be monitored for resistance. Data form treated orchards should then be compared with data from regions where oxytetracycline 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 oxytetracycline. 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 oxytetracycline 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 medium risk for creating an adverse human health impact. If the release and exposure assessments are high instead of medium because the lack of data on resistance is not considered as a mitigating factor and non-food exposure is included as KAW recommends in these comments, then the overall risk will be high. This means that more controls would be needed to mange the risk than suggested above. KAW requests that EPA take action to limit the use of this drug to appropriate uses given this medium level and potentially high risk to public health..

References

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