KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

www.KeepAntibioticsWorking.com



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Office of Pesticide Programs (OPP)
Regulatory Public Docket (7502P)
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Attention: Docket ID Number EPA-HQ-OPP-2006-0234
FRL-8370-8

Dear Sir or Madam,

Keep Antibiotics Working (KAW) (www.KeepAntibioticsWorking.com), a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups dedicated to eliminating a major cause of antimicrobial resistance the inappropriate use of antimicrobials in agriculture, objects on behalf of our over ten million members to the granting of the Section 18 registration and time limited tolerance for residues of gentamicin in/on apple. KAW objects to this Section 18 registration because of the serious risk to public health from antimicrobial resistance developing as a result of this action. The completely inadequate assessment of the antimicrobial resistance risk described in the registration memorandum data 7/21/2007 does nothing to allay this concern.

In contrast to the toxicological safety assessment, the resistance risk assessment is based on unsupported assumptions and contained significant methodological errors. Allowing the nontherapeutic use of gentamicin on 26,600 acres of apples without an adequate assessment of the risk to public health is unacceptable. KAW asks that the Section 18 registration be revoked until an assessment based on accepted risk assessment methodology and supported by adequate data finds an acceptable level of risk for this use of gentamicin on apples.

**Major Flaws in Risk Analysis**

The public health risk assessment on antimicrobial resistance carried out by EPA is described in the 3/21/2007 memorandum referring to registration #06M101 pages 26 to 29. EPA states that the approach to risk assessment is similar to that of the Food and Drug Administration's Guidance for Industry #152. KAW accepts that this is an appropriate risk analysis methodology for evaluating the safety of antibiotic pesticides used on food crops, but the complete absence of data supporting central assertions in the risk assessment and significant flaws in the way that the risk assessment methodology is applied make the outcome of the assessment outcome completely non-credible.

Under Guidance #152 the risk analysis framework is a structured process with 5 steps: 1) hazard characterization, 2) release assessment, 3) exposure assessment, 4) consequence assessment, and 5) risk

estimation. Guidance #152 also includes suggested risk management actions for different levels of estimated risk. In applying this framework to the pesticide use of gentamicin, the EPA makes serious errors at almost every step. There is no indication that EPA submitted this assessment to peer review and it is likely that such a review would have identified these significant errors.

Hazard Characterization

Under Guidance #152, hazard characterization is a step prior to risk assessment that describes the drug of concern and the bacteria species which could potentially impact human health were resistance to develop. The EPA assessment fails to identify what bacteria of concern are potentially on fruit or in orchards. It also fails to adequately characterize the drug in question along with known mechanisms of resistance. Gentamicin is in the same aminoglycoside antimicrobial class as streptomycin. The emergency exemption was requested because of widespread resistance to streptomycin in orchards. This fact should have been noted as part of the hazard characterization. There is significant published material on cross resistance between different aminoglycoside antibiotics and on associated mechanisms of resistance. This information should have been included in the hazard characterization.

Release Assessment

The release assessment under Guidance #152 is an estimate of "the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of resistant bacteria in the animal" and it has as its boundary the point of harvest. The EPA assessment describes the release assessment as the "probability that gentamicin-resistant bacteria are present in the commodity as a consequence of the pesticidal use" but does not clearly identify the boundary of the release assessment.

The EPA asserts that the release assessment is low, but cites no publications and provides no data supporting this assertion. If gentamicin is used like the antimicrobial streptomycin that it is replacing, then 6 to 10 applications could be applied spaced three to four days apart. This would result in a period of treatment from 18 to 40 days. Whole orchards are treated at once, not individual plants, and most orchards throughout the effected region will be treated. Under FDA's Guidance #152 this would be considered high extent of use because it lasts over 21 days and is not limited to individual treatments. KAW is aware of no studies of resistance selection in fruit crops, but this level of use in food animals would almost certainly select for resistant bacteria in the treated population even starting with totally susceptible bacteria. Without any data indicating otherwise, it is difficult to understand on what basis EPA believes that this level of use will not lead to increased resistance in bacteria in orchards and on fruit.

The release assessment also fails to consider how previous use of streptomycin may impact resistance to gentamicin in orchards. The release assessment does note that resistance to gentamicin can be transmitted on mobile elements thus increasing the risk.

In summary, the EPA identifies no data on how the use of gentamicin or any other antibiotic affects resistance in target organisms in orchards, but asserts that resistance would be low because gentamicin has so far not been used. Under Guidance #152, when there is no information available for a factor the default assumption is that the factor is high. The EPA in the absence of information assumes that this factor is low.

Given the available information that gentamicin is in the same class of antimicrobials as streptomycin, aminoglycoside resistance is widespread in orchards, gentamicin resistance is contained on mobile genetic elements, the antimicrobial pesticide will be used over long periods of time both orchard wide and region wide, and no studies are identified supporting the assertion that resistance will not develop under these

conditions, it is clear that the risk of release is high according to the methodology recommended in Guidance #152.

Exposure Assessment

Under Guidance #152, the exposure assessment "describes the likelihood of human exposure to food-borne bacteria of human health concern through particular exposure pathways." The bacteria of concern are both susceptible and resistant, because the release assessment already describes the likelihood that increased resistance will result from the antibiotic use. The EPA assessment confounds the release and exposure by stating that because the release is low the exposure is also necessarily low. This is a major methodological error that leads to a false estimate of risk. It is related to the failure by the assessors to adequately characterize the hazard and the failure to identify the boundaries of the release assessment. The hazard characterization should have identified bacteria of concern and the exposure assessment should then have considered at what levels are they present at harvest and during consumption. Instead, the EPA in the exposure assessment states "gentamicin has not been used as a plant agricultural antibiotic so there has been no selection pressure which would result in resistant bacteria." First this is what the release assessment is to determine, and second the question to be answered is what is the impact of the proposed use, not the impact of the prior non-use. The finding of a low exposure risk is also inconsistent with the findings of medium risk in the EPA evaluations of oxytetracycline and streptomycin antimicrobial resistance risk.

The exposure assessment should also consider that apples unlike animal products are often consumed raw and unpasteurized. Because of this, much lower levels of contamination create the same risk.

Beyond the methodological error of confounding the release and exposure assessment, the EPA assessors provide no data supporting their finding of low exposure. There are studies available of bacterial contamination of fruit at time of harvest. These have been mainly carried out to determine the risk of contaminants in cider and juice production. Again applying the dictum in Guidance #152 that a factor should be considered high when there is insufficient information to make a decision, the outcome of the release assessment should be high.

Consequence Assessment

Under Guidance #152, the consequence assessment is based on the medical importance of the drug to which resistance develops. FDA considers gentamicin highly important in respect to veterinary antimicrobial drug use because of its important in treating enteroccocal endocarditis. EPA uses the same level of medical importance as FDA. This differs from the World Health Organization (WHO) which considers gentamicin to be critically important because of the potential to transfer resistant enteroccoci from animal to humans. It is not entirely appropriate to use either the FDA or the WHO list for this purpose, because they were created to determine the risk of pathogens coming from animals and not food crops.

Risk Estimation

Under Guidance #152, the overall risk estimation is made by integrating the release, exposure, and consequence assessments. The EPA uses the same method including Table 6 in Guidance #152 to integrate the 3 parts (release, exposure, and consequence). The use of this table in this way by EPA is totally inappropriate because of the confounding between the release and exposure estimates. The EPA uses the low release assessment to determine that the exposure estimate is also low essentially double counting the low finding in the release assessment. The FDA table was designed for separate release and

exposure elements, so this use of it is inappropriate. The use of Table 6 when there is no data supporting the findings in two out of three (release and exposure) parts of the assessment is also not justifiable.

Risk Management

If either the release or exposure assessments are high as KAW believes they should be, then the overall risk estimation would be medium. If both were high then the risk estimation would be high. In either case, high or medium, the risk management recommendations in Guidance #152 would be against using this antimicrobial over such a long period of time at an orchard wide level.

## Conclusion

Given the serious methodological flaws and significant data gaps, KAW requests the EPA revoke the Section 18 registration and time limited tolerance for residues of gentamicin in/on apple. KAW also strongly recommends that EPA seek outside review of all its activities related to antimicrobial resistance risk assessment. The serious flaws identified in the gentamicin risk assessment indicate that the agency needs to reevaluate its approach for assessing this important public health risk. Finally, KAW asks that the EPA consider whether it is appropriate to respond to a problem of antimicrobial resistance in plants by allowing the use of another antimicrobial in the same class that has even more important applications in human medicine. If it were just plant health at issue here, it might make sense, but when public health is at risk this action seems extremely unwise.