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Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
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Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Oxytetracycline

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

June 30, 2006

CERTIFIED MAIL

Dear Registrant:

This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision for Oxytetracycline," which was approved on June 30, 2006. This document is also known as a Tolerance Reassessment Decision, or TRED. A Notice of Availability of this tolerance reassessment decision will be published in the *Federal Register*. Because of the extensive collaboration with registrants and other federal agencies prior to and during the 60-day public comment period and because relatively few comments were received during the 60-day public comment period, the TRED document and final risk assessments are being issued without an additional public comment period. The TRED, supporting risk assessments, and response to comments for oxytetracycline are available to the public in EPA's Pesticide Docket EPA-HQ-OPP-2005-0492 at: http://www.regulations.gov. EPA issued a reregistration eligibility decision for oxytetracycline in March 1993.

The oxytetracycline TRED was developed through EPA's public participation process, published in the Federal Register on May 14, 2004, which provides opportunities for public involvement in EPA's pesticide tolerance reassessment and reregistration programs. Developed in partnership with USDA and with input from EPA's advisory committees and others, the public participation process encourages public involvement starting early and continuing throughout the pesticide risk assessment and risk mitigation decision making process. The public participation process encompasses full, modified, and streamlined versions that enable EPA to tailor the level of review to the level of refinement of the risk assessments, as well as to the amount of use, risk, public concern, and complexity associated with each pesticide. Through the public participation process, EPA is making a commitment to both involve the public and meet statutory deadlines.

Background

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires EPA to reassess all the tolerances in effect on or before the enactment of FQPA on August 3, 1996. In reassessing these tolerances, EPA must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. Once a safety finding has been made,

the tolerances are considered reassessed. Existing tolerances associated with oxytetracycline have been reassessed in accordance with FFDCA, as amended by FQPA.

In addition to the assessment of direct risks posed by dietary exposure, EPA also assessed the potential for pesticidal uses of oxytetracycline to contribute to antibiotic resistance. In late 2004, EPA held an internal "problem formulation" meeting for the streptomycin and oxytetracycline TREDs. During this meeting EPA noted that these chemicals' potential contributions to antibiotic resistance were not fully understood. Recognizing that pesticidal uses of streptomycin and/or oxytetracycline may possibly contribute to antibiotic resistance of bacterial pathogens with potential adverse public health consequences, and that other entities may have more expertise in evaluating antibiotic resistance, EPA requested input from three other agencies.

In May 2005, EPA hosted two conference calls with U.S. Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research and Center (CDER) and Center for Veterinary Medicine (CVM), and U.S. Department of Agriculture (USDA) to discuss antibiotic resistance. EPA then met internally to discuss the options for addressing potential concerns resulting from the continued use of antibiotics as pesticides and evaluate the appropriateness and feasibility of conducting a qualitative antibiotic resistance risk assessment based on FDA CVM's Guidance for Industry #152 (Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern). Based on the discussion and evaluation, EPA included in its risk assessments a qualitative assessment of antibiotic resistance modeled on FDA CVM's Guidance for Industry #152 (see the Streptomycin HED Chapter dated February 7, 2006 and the Oxytetracycline HED Chapter dated June 19, 2006).

In February 2006, EPA opened a 60-day public comment period for the preliminary risk assessments. During the public comment period, EPA received 8 comments relating to the use of oxytetracycline. Comments were received from Rutgers University, U.S. Apple Association, Northwest Horticultural Council, Keep Antibiotics Working, and 4 plant pathologists from around the U.S. The majority of the respondents were supportive of the use of oxytetracycline on fruit trees and indicated that it is an integral and critical component in disease control programs. Another respondent urged EPA to implement steps to minimize the potential contribution to antibiotic resistance from the use of oxytetracycline. All of these comments were considered and incorporated into EPA's risk management decisions and this document represents EPA's response to public comments.

EPA has completed its review of the dietary risks and is issuing its risk management decision for oxytetracycline.

Regulatory Decision

EPA has evaluated the dietary and residential risks from the supported registered uses and has determined that there is a reasonable certainty that no harm to any population subgroup will result from exposure to oxytetracycline.

Acute dietary exposure was not estimated because no acute toxicity was identified in any of the relevant studies in the oxytetracycline database. The chronic dietary exposure estimate (food + water) for the U.S. population is 32% of the chronic Population Adjusted Dose (cPAD). The chronic dietary exposure estimate for the most highly exposed population subgroup, all infants (children <1 year of age), is 95% of the cPAD using conservative, screening level exposure assumptions. Dietary risk estimates for food and water are below EPA's level of concern.

The 2 tolerances currently established at 40 CFR 180.337 for residues of oxytetracycline in/on raw agricultural commodities are now considered reassessed under section 408(q) of the FFDCA (see Table 6).

Use Profile

Oxytetracycline (Case Number 0655) includes the active ingredients oxytetracycline (PC Code 006304), hydroxytetracycline monohydrochloride (PC Code 006308), and oxytetracycline calcium (PC Code 006321). In this document, unless specified otherwise, "oxytetracycline" refers to both oxytetracycline hydrochloride and oxytetracycline calcium; there is no active product for PC Code 006304.

Table 1. Chemicals in Case Number 0655

PC Code	Chemical Name
006304	oxytetracycline, a.k.a. 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-, (4S-(4.alpha.,4a.alpha.,5.alpha.,5a.alpha.,6.beta.,12a.alpha.))-
006308	oxytetracycline hydrochloride, a.k.a. hydroxytetracycline monohydrochloride
006321	oxytetracycline calcium, a.k.a. calcium oxytetracycline

Oxytetracycline is an antibiotic pesticide used to control bacteria, fungi, and mycoplasma-like organisms. The majority of oxytetracycline is used on pears. Other crops treated include peaches, nectarines, and apples. Oxytetracycline use on apples has been approved under emergency exemption (Section 18) for several years due to the lack of efficacious alternatives. A full registration (Section 3) is currently under review by EPA as a separate action. Oxytetracycline is also registered for use on forest trees and ornamental trees, shrubs, and vines. The estimated total domestic pesticidal use (annual average) is approximately 15,000 lbs. active ingredient (ai) per year. Approximately 8,000 lbs. ai are used annually on pears and 2,000 lbs. ai are used annually on peaches, and 2,000 lbs. ai are used annually on apples. All other uses are less than 500 lbs. ai annually. There are no residential pesticidal uses of oxytetracycline. Oxytetracycline is

also registered with FDA to treat infectious diseases in animals and humans and also as a food additive to increase animal weight gain. Although firm estimates are not available, literature studies report that the estimated percentage of antibiotics applied to plants compared to all other antibiotic use is <0.5% (McManus, 2002).

Oxytetracycline is typically applied to foliage by ground or aerial spray, and is also used as a tree injection. Oxytetracycline may be used every 4 to 6 days and up to 10 times per season depending on crop type and application method.

Alternative Control Measures:

Oxytetracycline is one of few tools available to combat fire blight, a potentially devastating disease in fruit trees. Non-antibiotic alternatives include copper, prohexadione, biological controls, fosetyl-Al, pruning, and planting resistant cultivars. Antibiotic alternatives include streptomycin.

Copper: Copper provides reasonable protection against fire blight disease if applied as preventive sprays in combination with use of disease forecasting models. Copper is effective in reducing the percent of infected blossom cluster infections on apples. The efficacy of copper is dependent upon many factors such as disease pressure, application timing, and its persistence on plant surfaces. The persistence is dependent upon weather conditions. In current disease management, copper plays an important part in a fire blight management program, but can only be safely applied in the early spring or autumn when the trees are dormant.

Prohexadione: Prohexadione® has no pesticidal properties. It reduces linear growth of branches resulting in reduced tree canopy volume. Prohexadione treatment of trees reduces their susceptibility to fire blight. It may be an additional tool in the management of fire blight.

Biological Control Agent: BlightBan® (a.i. *Pseudomonas fluorescens* strain A506) is used to complement streptomycin (see below); it is not a replacement for streptomycin and other antibiotics. Commercial use of Blightban is limited due to poor efficacy and high cost.

Fosetyl-Al: Aliette®, a fungicide, is also registered for fire blight control, but data supporting this use are not convincing of its efficacy against fire blight. No practical control activity was observed in experimental trials in Michigan. Fosetyl-Al is not used commercially for the control of fire blight because it does not appear to be efficacious.

Pruning: The branches and tree limbs that show fire blight disease symptoms in the late season are removed from the trees and destroyed to prevent the spread of disease and source of inoculums for the next year. This practice is effective in reducing the primary inoculums and tree death.

Resistant Cultivars: Red Delicious variety of apple has some resistance against the fire blight disease but it is not grown widely because most consumers prefer other varieties. All other commercially grown varieties are susceptible.

Streptomycin: Streptomycin is a registered antibiotic for the control of fire blight, but in some areas the pathogen has developed resistance to the antibiotic.

Human Health Effects

(For a complete discussion, see the Oxytetracycline HED Chapter dated June 19, 2006.)

No acute dietary endpoint was selected because no acute toxicity was identified in any of the relevant studies in the oxytetracycline database.

The chronic dietary endpoint for all populations is based on microbiological effects observed in a resistance study in dogs at the lowest observed adverse effect level (LOAEL) of 0.25 mg/kg/day. The no observed adverse effect level (NOAEL) in this study was 0.05 mg/kg/day. An uncertainty factor of 100 (10X for intra-species variation and 10X for inter-species extrapolation) was applied to the NOAEL resulting in a chronic reference dose (cRfD) of 0.0005 mg/kg/day. A summary of the toxicological dose and endpoints for oxytetracycline that were used in the dietary risk assessment is shown below in Table 2.

Table 2. Toxicological Dose and Endpoints used in the Dietary Risk Assessment

Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary	N/A - toxicity attributable to acute exposure was not identified		
Chronic Dietary (All populations)	NOAEL= 0.05 mg/kg/day UF = 100 **cRfD[1] = 0.0005 mg/kg/day**	FQPA SF = 1X **cPAD[2] = 0.0005 mg/kg/day**	Microbial study in dogs LOAEL = 0.25 mg/kg/day based on microbial effects
Cancer	Not Classifiable as to Human Carcinogenicity[3]		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, chronic RfD = chronic reference dose, N/A = not applicable

[1] $cRfD = \frac{NOAEL}{UF}$

[2] $cPAD = \frac{cRfD}{FQPA\ SF}$

[3] No evidence of carcinogenicity was found in a literature search of toxicity in animals. In the mouse, there was no evidence of carcinogenicity at the highest dose tested in the carcinogenicity study. In the rat carcinogenicity study, only benign tumors were observed. Therefore, there is low concern for carcinogenicity and no quantitative assessment is required.

The drug oxytetracycline is administered to humans orally or intravenously to treat infectious diseases caused by a wide variety of microorganisms. The dose for adults

is approximately 15 to 30 mg/kg. The daily dose for children is approximately 25 to 50 mg/kg.

There is no evidence of increased sensitivity in pups versus adults based on rat and mouse developmental studies and the rat multi-generation reproduction study. In prenatal developmental studies in both rats and mice treated with oxytetracycline, there was no toxicity identified in the pups at any dose tested. In the two-generation study, there was no toxicity identified in pups at the highest dose tested (18 mg/kg/day). The degree of concern is low for pre- and/or post-natal toxicity resulting from exposure to oxytetracycline and the special FQPA SF can be reduced (1X) since there are no residual uncertainties for pre- and/or post-natal toxicity.

The dose used in human medicine ranges from 1000 mg to 2000 mg per day (orally or intravenously). Based on the dose used in human medicine, a theoretical NOAEL of 16.7 mg/kg/day could be calculated by dividing the dose (1000 mg/day) by the approximate weight of an adult (60 kg). This theoretical NOAEL could then be used to derive a cRfD to estimate dietary risk. Instead of deriving the cRfD from a theoretical NOAEL based on human drug use, EPA used the NOAEL of 0.05 mg/kg/day in dogs to derive the cRfD and cPAD of 0.0005 mg/kg/day. Since the cPAD derived from the chronic RfD is several orders of magnitude lower than the dose that would be derived from using the theoretical human NOAEL, the cRfD is protective for all effects and is not likely to underestimate exposure. There are no further residual uncertainties and the FQPA safety factor can be removed (1X).

Oxytetracycline has a low acute toxicity (Category IV) for oral toxicity in mice ($LD_{50} > 7200$ mg/kg). Based on the availability of extensive information from oxytetracycline use as a human drug, the data requirements for the acute dermal, inhalation, primary eye irritation, and skin sensitization studies in animals have been waived.

No evidence of carcinogenicity was found in a literature search of toxicity in animals. However, in accordance with EPA’s Guidelines for Carcinogen Risk Assessment, oxytetracycline is classified as “Not Classifiable as to Human Carcinogenicity” due to the lack of guideline carcinogenicity studies.

EPA's use of information derived from the pharmaceutical uses of streptomycin is in accordance with EPA's Final Rule promulgated on January 26, 2006 related to Protection for Subjects in Human Research, which is codified in 40 CFR Part 26.

Drinking Water Exposure and Risk Assessment

(For a complete discussion, see the Oxytetracycline Tier 1 Drinking Water Assessment dated May 22, 2006.)

Drinking water exposure to pesticides can occur through ground and surface water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking

water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. Since available water monitoring data are considered inadequate to determine surface and ground water drinking water exposure estimates, estimated drinking water concentrations (EDWCs) are calculated from surface and ground water models FIRST V 1.0 and SCI-GROW V 2.3, respectively. The EDWCs are based on application methods, rates, and use sites that would likely yield the highest drinking water concentrations.

Table 3 presents Tier 1 (screening level) chronic EDWCs for surface water and groundwater assuming nine separate applications of oxytetracycline calcium to peaches and/or nectarines at a rate of 0.64 lb ai/A with a 7-day retreatment interval.

Table 3. Highest surface/ground water EDWCs for oxytetracycline

Exposure Duration	Surface Water Chronic EDWC	Ground Water EDWC
Chronic	4.6 ppb	0.033 ppb

Concentrations in surface water (4.6 ppb) and ground water (0.033 ppb) represent upper-bound estimates of the concentrations that might be found in surface water and groundwater due to the use of oxytetracycline calcium on peaches/nectarines. These drinking water exposure estimates are incorporated into an aggregate chronic dietary assessment using both food and water concentrations.

Acute and Chronic Dietary (Food + Water) Exposure and Risk Assessment

(For a complete discussion, see the Oxytetracycline Chronic Dietary Exposure Assessment dated February 6, 2006.)

Acute dietary risk assessments were not conducted because no toxicity attributable to acute exposure could be identified based on the data currently available for oxytetracycline.

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™), Version 2.03, which used food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Based on the registered uses of oxytetracycline on pears, peaches, and nectarines, and the proposed Section 3 use on apples, no quantifiable residues in meat, milk, poultry, and eggs (MMPE) are expected. However, FDA has established tolerances in MMPE commodities for the sum of the residues of the tetracyclines including chlortetracycline, oxytetracycline, and tetracycline as listed in 21 CFR 556.500. Accordingly, EPA's dietary analysis includes estimates of possible oxytetracycline residues in livestock commodities making use of monitoring data from the Food Safety and Inspection Service (FSIS) collected in 2002, 2003, and 2004. These data were taken from the FSIS National Residue Program Data publications (Red Books).

The relevant FSIS data sampled kidney tissue from a variety of livestock (cattle, swine, poultry, goats, etc), analyzing for oxytetracycline residues. As tetracycline residues partition preferentially into fat and kidney, measured oxytetracycline residues in kidney were used as worst-case level for all other livestock tissues. In 2004 and 2002, no oxytetracycline residues were detected in 4270 and 6942 samples, respectively. In 2003, three kidney samples had finite oxytetracycline residue levels out of 5260 samples. To compute an estimated residue level for use in DEEM-FCID, an average residue level was calculated using ½ level of detection for nondetects (0.005 ppm) together with the three detected levels of 2.5, 5.0, and 5.0 ppm. This provided a conservative estimated residue level of oxytetracycline in livestock commodities of 0.0058 ppm and this value was used for all livestock commodities in the DEEM-FCID analyses.

The chronic dietary assessments assumed tolerance level residues on treated crops and incorporated percent crop treated information. Modeled EDWCs for surface water sources were also included. The highest exposure and risk estimates were for all infants (<1 year old) using surface water as the drinking water source. The exposure for all infants was 0.000473 mg/kg/day, which utilized 95% of the cPAD. The chronic dietary exposure estimates for food and water are below EPA's level of concern (see Table 4).

Table 4. Summary of Dietary (Food + Water) Exposure and Risk

Population Subgroup	cPAD (mg/kg/day)	Surface Water		
		EDWC (ppb)	Total (Food + Water) Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.0005	4.6	0.000160	32
All Infants (< 1 year old)	0.0005	4.6	0.000473	95

EDWC = estimated drinking water concentration, cPAD = chronic population adjusted dose

Residential Risk

At this time, no product containing oxytetracycline is registered for residential use and there is no anticipated exposure in or around homes or recreational areas.

Aggregate Risk

(For a complete discussion, see the Oxytetracycline HED Chapter dated June 19, 2006.)

In accordance with the FQPA, EPA must consider and aggregate pesticide exposures and risks from all potential sources including food, drinking water, and residential exposures. Since no product containing oxytetracycline is registered for residential use, only food and drinking water were considered in the aggregate assessment. In an aggregate assessment, exposures are combined and compared to quantitative estimates of hazard (e.g., a NOAEL). When aggregating exposures and risks from various sources, EPA considers both the route and duration of exposure. In general, exposures from various sources are aggregated only when the toxic effect determined by the endpoint selected for each route is the same. In the case of oxytetracycline, an

aggregate assessment was performed using high-end exposures and conservative endpoints. Further refinements would have been incorporated into the risk assessment if exposures of concern had been identified. Since the screening level aggregate assessment did not show risks of concern, EPA concludes with reasonable certainty that combined residues of oxytetracycline from food and drinking water exposures will not result in an aggregate risk of concern to any population subgroup.

An acute aggregate assessment was not conducted because acute toxicological effects attributable to oxytetracycline could not be identified. Short-term and intermediate-term aggregate risk assessments were not conducted because there are no existing or proposed residential uses for oxytetracycline.

A chronic aggregate assessment for food and water exposure was conducted because a chronic toxicological endpoint was identified for oxytetracycline. EPA's aggregate assessment for food includes estimates of possible oxytetracycline residues in livestock commodities making use of monitoring data from the Food Safety and Inspection Service (FSIS) National Residue Program Data collected in 2002, 2003, and 2004. The highest aggregate exposure and risk estimates were for all infants (<1 year old) using surface water as the drinking water source, which utilized 95% of the cPAD. The chronic dietary exposure estimates for food and water are below EPA's level of concern. Results of the dietary (food + drinking water) exposure and risk assessment are presented in Table 4.

Pharmaceutical Aggregate Risk

Section 408 of the FFDCA requires EPA to consider potential sources of exposure to a pesticide and related substances in addition to the dietary sources expected to result from a pesticide use subject to the tolerance. In order to determine whether to maintain a pesticide tolerance, EPA must "determine that there is a reasonable certainty of no harm." Under FFDCA section 505, the Food and Drug Administration reviews human drugs for safety and effectiveness and may approve a drug notwithstanding the possibility that some users may experience adverse side effects. EPA does not believe that, for purposes of the section 408 dietary risk assessment, it is compelled to treat a pharmaceutical user the same as a non-user, or to assume that combined exposures to pesticide and pharmaceutical residues that lead to a physiological effect in the user constitutes "harm" under the meaning of section 408 of the FFDCA.

Rather, EPA believes the appropriate way to consider the pharmaceutical use of oxytetracycline in its risk assessment is to examine the impact that the additional non-occupational pesticide exposures would have to a pharmaceutical user exposed to a related (or, in some cases, the same) compound. Where the additional pesticide exposure has no more than a minimal impact on the pharmaceutical user, EPA could make a reasonable certainty of no harm finding for the pesticide tolerances of that compound under section 408 of the FFDCA. If the potential impact on the pharmaceutical user as a result of co-exposure from pesticide use is more than minimal, then EPA would not be able to conclude that dietary residues were safe, and would need to discuss with FDA

appropriate measures to reduce exposure from one or both sources. EPA provided its findings with respect to oxytetracycline to FDA in a letter dated May 24, 2006, which is available in the public docket (EPA-HQ-OPP-2005-0492).

The pesticidal exposure estimates described in the May 24, 2006 letter reflect the dietary dose from pesticidal uses of oxytetracycline that a user treated with a pharmaceutical oxytetracycline product would receive in a reasonable worst-case scenario. EPA's pesticide exposure assessment has taken into consideration the appropriate population, exposure route, and exposure duration for comparison with exposure to the pharmaceutical use of oxytetracycline.

EPA estimates that the pharmaceutical oxytetracycline exposure a user is expected to receive from a typical therapeutic dose (25 mg/kg/day for children) is 50,000 to 200,000 times greater than the estimated dietary exposure from the pesticidal sources of oxytetracycline (0.000121 mg/kg/day to 0.000473 mg/kg/day). Therefore, because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA believes that there is a reasonable certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with oxytetracycline. FDA is aware of EPA's conclusions regarding pesticide exposure in users receiving treatment with a pharmaceutical oxytetracycline drug product and FDA's June 7, 2006 response to EPA is available the public docket (EPA-HQ-OPP-2005-0492).

Cumulative Risk Assessment

FQPA requires that EPA consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency considers other substances because low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the other substances individually.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to oxytetracycline and any other substances, and oxytetracycline does not appear to produce a toxic metabolite that is also produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that oxytetracycline has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Tolerance Reassessment Summary

Tolerances for the pesticidal residues of oxytetracycline are established under 40 CFR 180.337. A summary of the oxytetracycline tolerance reassessment is presented in Table 5.

Table 5. Tolerance Reassessment Summary for Oxytetracycline

Commodity	Current Tolerance (ppm)	Reassessed Tolerances (ppm)	Comments
Tolerances Under 40 CFR §180.337			
Peach	0.35	0.35	
Pear	0.35	0.35	
Tolerances To Be Proposed Under 40 CFR §180.337			
Apple	None	0.35	EPA has adequate data to support apple.

FDA has established tolerances for the sum of the tetracyclines (chlortetracycline, oxytetracycline, tetracycline) residues for beef cattle, dairy cattle, calves, swine, sheep, chickens, turkeys, finfish, and lobster as listed under 21 CFR Part 556.500. These tolerances are regulated by FDA and are not included in this tolerance reassessment decision; however, the residues from these uses were included in EPA's dietary risk assessment.

Antibiotic Resistance

(For a complete discussion, see the Oxytetracycline HED Chapter dated June 19, 2006.)

Bacterial resistance to oxytetracycline as a result of drug use has long been recognized. EPA recognizes that pesticidal uses of oxytetracycline may contribute to antibiotic resistance of bacterial pathogens with potential adverse public health consequences. After evaluating available data and consulting with CDC, FDA CDER, FDA CVM, and USDA, EPA determined that insufficient data were available to conduct a quantitative antibiotic resistance assessment and instead conducted a qualitative antibiotic resistance assessment based on FDA CVM's Guidance for Industry #152.

Because anticipated dietary residues are extremely low (conservatively estimated at 0.000160 mg/kg/day for the General U.S. Population), it is unlikely that antibiotic resistance from pesticidal use of oxytetracycline would result from food exposure. Bacterial resistance to oxytetracycline from pesticidal use of oxytetracycline with adverse public health consequences could theoretically occur from (1) development of resistance in bacterial pathogens present in orchards or (2) from development of resistance from non-pathogenic bacteria in orchards which later transferred their resistance to human bacterial pathogens.

The possibility of antibiotic resistance resulting in adverse human health consequences is determined principally by the likelihood of non-pathogenic organisms in orchards transferring their resistance to pathogens in the human environment. Antibiotic resistance from pesticidal use of oxytetracycline is unlikely to result directly from dietary

residues of oxytetracycline because dietary residues are very low. The maximum aggregate dietary exposure was 0.000473 mg/kg/day which is very small when compared to a 25 mg/kg/day drug dose. The drug dose is 50,000 times greater than the estimated pesticidal dietary exposure. The small dose from pesticidal exposure would not be expected to select for resistant bacteria because very few bacteria would be killed by this small dose. If bacterial resistance to oxytetracycline from pesticidal use occurs, it is most likely that it would be caused by development of resistance from non-pathogenic bacteria in orchards which later transferred their resistance to human bacterial pathogens.

In setting or revising tolerances under section 408 of the FFDCA, EPA must determine that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue." Because the risk of antibiotic resistance does not arise from the ingestion of pesticide residues, the risk has not been aggregated for the purposes of this action. EPA may consider the risk of antibiotic resistance in future actions such as registration review or approval of new uses for oxytetracycline. EPA is requiring use and usage information as well as additional environmental fate data to address the uncertainties regarding potential antibiotic resistance from the pesticidal uses (see Table 6). Based on these new data, EPA may also require an antibiotic resistance monitoring study to be conducted in orchards or other high use areas. This study is held in reserve and, if deemed appropriate, will be required through a separate data call-in. Additional label statements will also be required that will ensure judicious use of oxytetracycline.

Additional Generic Data Requirements

Toxicity for oxytetracycline was assessed using the extensive database for oxytetracycline from its use as a human drug and using animal toxicity studies submitted to FDA. Toxicological and environmental fate data requirements were waived for oxytetracycline in the 1993 RED. Since the RED, EPA has become aware of the increasing importance of antibiotic resistance. Therefore, the following environmental fate and use data requirements presented in Table 6 are necessary to better understand the fate of pesticidal oxytetracycline in the environment and to support the continued registration of oxytetracycline.

Table 6. Oxytetracycline Generic Data Requirements

Guideline	Study Title
810.1000	Use and Usage Information
810.1000	Antibiotic Resistance in Orchards[1]
835.2120	Hydrolysis of Parent and Degradates as a Function of pH at 25°C
835.2240	Direct Photolysis Rate of Parent and Degradates in Water
835.2410	Photodegradation of Parent and Degradates in Soil
835.4100	Aerobic Soil Metabolism
835.4200	Anaerobic Soil Metabolism
835.4400	Anaerobic Aquatic Metabolism
835.4300	Aerobic Aquatic Metabolism
835.1240	Soil Column Leaching
835.1410	Laboratory Volatilization from Soil

Guideline	Study Title
835.6100	Terrestrial Field Dissipation
850.1730	Fish BCF
860.1340	Analytical Enforcement Method

[1] Based on the results of the required environmental fate data, EPA may require a special study to be conducted on antibiotic resistance in orchards. This study is being held in reserve and, if deemed appropriate, will be required through a separate data call-in.

Required Label Changes

Table 7 presents the label amendments required for all products containing oxytetracycline.

Table 7. Oxytetracycline Label Changes Summary Table

Description	Amended Labeling Language	Placement on Label
General Application Restrictions	"This product contains the antibiotic oxytetracycline. To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other antibacterial products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria."	Directions for Use
General Application Restrictions	"This material is not to be used for medical or veterinary purposes."	Directions for Use

Conclusions

EPA has evaluated the dietary risks from the supported registered uses and has determined that there is a reasonable certainty that no harm to any population subgroup will result from chronic exposure to oxytetracycline and considers the existing tolerances reassessed. Although not related to the FQPA safety finding, there are uncertainties about the pesticidal contributions to antibiotic resistance. To better understand the fate of pesticidal oxytetracycline in the environment and its potential contribution to antibiotic resistance, EPA is requiring additional use and environmental fate data. EPA is also requiring label amendments that will ensure judicious use of oxytetracycline.

Please contact Lance Wormell of my staff with any questions regarding this decision. He may be reached by phone at (703) 603-0523 or by e-mail at wormell.lance@epa.gov.

Sincerely,

Debra Edwards, Ph.D., Director
Special Review and Reregistration Division

Technical Support Documents for the Oxytetracycline TRED

1. William Donovan and Kimyata Morgan (USEPA/OPPTS/OPP/HED). Oxytetracycline: HED Chapter of the Tolerance Reregistration Eligibility Decision Document (TRED) and Proposed New Uses on Apples. Revised After Phase 3 Public Comments. DP Barcode D330129. June 19, 2006.

2. William H. Donovan (USEPA/OPPTS/OPP/HED). Oxytetracycline Tolerance Reregistration Eligibility Decision (TRED). Summary of Product Chemistry and Residue Data. DP Barcode D315689. September 27, 2005.

3. William H. Donovan (USEPA/OPPTS/OPP/HED). Oxytetracycline Chronic Dietary Exposure Assessment for the Tolerance Reregistration Eligibility Decision (TRED). Revised After Phase 1-Error Only Corrections. DP Barcode D315686. February 6, 2006.

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