United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7508P)

EPA 738-R-06-012
June 2006

Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Streptomycin

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 Streptomycin," 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 streptomycin are available to the public in EPA's Pesticide Docket EPA-HQ-OPP-2005-0493 at: http://www.regulations.gov. EPA issued a reregistration eligibility decision for streptomycin in September 1992.

The streptomycin 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 streptomycin 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 streptomycin 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 9 comments relating to the use of streptomycin. Comments were received from U.S. Apple Association, Michigan State University, Virginia Polytechnic and State University, 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 streptomycin on fruit trees and ornamentals 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 streptomycin. 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 and residential risks and is issuing its risk management decision for streptomycin.

Regulatory Decision

EPA has evaluated the aggregate 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 streptomycin.

Acute dietary exposure was not estimated because no acute toxicity was identified in any of the relevant studies in the streptomycin database. The chronic dietary exposure estimate (food + water) for the U.S. population is 4% 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 9% of the cPAD. Dietary risk estimates for food and water are below EPA's level of concern. This assessment is considered conservative since tolerance level residues and screening level water estimates were included in the dietary assessment; however percent crop treated information was incorporated.

The inhaled chronic exposure estimate from homeowner application to fruit trees and shrubs using a low-pressure handwand (0.000067 mg/kg/day) is below EPA's level of concern (margin of exposure = 75,000).

The chronic aggregate (dietary + residential) risk estimate is below EPA's level of concern. The highest exposure from food and water was for all infants (9% of the cPAD). When EPA aggregated inhalation exposure (0.000067 mg/kg/day) and dietary exposure for the General U.S. Population (0.001980 mg/kg/day), the increment in exposure was minimal; therefore, aggregate risk is below EPA's level of concern. Exposure from dermal absorption is also expected to be minimal.

The 5 tolerances currently established at 40 CFR 180.245 for residues of streptomycin in/on raw agricultural commodities are now considered reassessed under section 408(q) of the FFDCA (see Table 6). In addition, EPA will propose two new tolerances for dry and succulent bean under 40 CFR §180.245(a)(1).

Use Profile

Streptomycin (Case Number 0169) includes the active ingredients streptomycin (PC Code 006306) and streptomycin sulfate (PC Code 006310). Most end-use products express both streptomycin sulfate and pure streptomycin content. In this document, "streptomycin" refers to both streptomycin and streptomycin sulfate.

Table 1. Chemicals in Case Number 0169

PC Code	Chemical Name
006306	streptomycin, a.k.a. D-Streptamine, O-2-deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1->2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1->4)-N,N'-bis(aminomethyl)-
006310	streptomycin sulfate

Streptomycin is an antibiotic pesticide used to control bacterial diseases in certain fruits, vegetables, seeds, and ornamental crops. The majority of streptomycin is used on apples and pears. Other crops treated include celery, philodendron, tomato, peppers, dieffenbachia cuttings, chrysanthemums, roses, pyracantha, potatoes, and tobacco. The estimated total domestic pesticidal use (annual average) is approximately 20,000 lbs. active ingredient (ai) per year. Approximately 10,000 lbs. ai are used annually on apples and 7,000 lbs. ai are used annually on pears. All other uses are less than 500 lbs. ai annually. Streptomycin is also registered with FDA to treat infectious diseases in animals and humans. 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).

Streptomycin is typically applied by ground or aerial spray and is also used as a liquid soak, dust treatment, and seed treatment. Spray applications are generally made in the spring according to weather and crop development. If conditions are favorable for fire blight, streptomycin may be used every 3 to 4 days, 5 to 7 days, or 10 to 14 days depending on crop type and application method.

Alternative Control Measures:

Streptomycin 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 oxytetracycline.

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.

Oxytetracycline: Oxytetracycline is a registered antibiotic for the control of fire blight. Oxytetracycline has been used under emergency exemption in controlling fire blight disease on apples.

Human Health Effects

(For a complete discussion, see the Streptomycin HED Chapter dated February 7, 2006.)

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

The chronic dietary endpoint for all populations is based on decreased body weight gain observed in a 2-year rat feeding study at the LOAEL of 10 mg/kg/day. The NOAEL in this study was 5 mg/kg/day. An uncertainty factor of 100 (10X for inter-species extrapolation and 10X for intra-species variation) was applied to the NOAEL resulting in a chronic reference dose (cRfD) of 0.05 mg/kg/day. The 2-year rat feeding study endpoint was used by FDA to set tolerances for animal drug residues of streptomycin in meat, by the World Health Organization to evaluate safety of streptomycin drug residues in meat, and by EPA in the 1992 streptomycin RED.

A summary of the toxicological dose and endpoints for streptomycin 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		

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= 5 mg/kg/day UF = 100 **cRfD[1] = 0.05 mg/kg/day**	FQPA SF = 1X **cPAD[2] = 0.05 mg/kg/day**	2-year feeding study in rats LOAEL = 10 mg/kg/day based on reduced body weight gain
Cancer	Inadequate Information to Assess Carcinogenic Potential[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. The report of the FDA 2-year feeding study in rats did not report evidence of tumors; however, not enough information was available in the summary to determine whether all required tissues were examined microscopically. A carcinogenicity study in mice was not available.

For the first 30 years of its use, the drug streptomycin was frequently used to treat pregnant women. It is now known that children may be born with hearing loss or inner ear problems from treatment of the mother with streptomycin during pregnancy. It is possible that the developing fetus is more sensitive than the mother to streptomycin-induced inner ear toxicity. Some children of mothers treated during pregnancy with streptomycin were born with hearing deficits, while the mothers presumably did not show evidence of hearing loss during treatment. However, these effects occurred after treatment at pharmacological doses of approximately 15 mg/kg/day by intramuscular injection. This corresponds to approximately 1500 mg/kg/day by the oral route, with 1% oral absorption, which is much higher than the oral NOAEL of 5 mg/kg/day selected for chronic dietary exposure. Other teratogenic effects were not attributed to prenatal streptomycin exposure and no teratogenic effects were noted in a rabbit developmental study at the high dose of 10 mg/kg/day. Therefore, there is no residual uncertainty for pre and/or post natal toxicity. Because the dose selected for risk assessment (5 mg/kg/day) is much lower than the injected dose at which potential susceptibility occurs (1500 mg/kg/day) in humans, and because of the adequacy of the exposure database, there are no residual concerns and the FQPA safety factor can be reduced to 1X.

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, streptomycin is classified as "Inadequate Information to Assess Carcinogenic Potential" due to the lack of guideline carcinogenicity studies. The report of the FDA 2-year feeding study in rats did not report evidence of tumors; however, not enough information was available in the summary to determine whether all required tissues were examined microscopically.

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 Streptomycin Chronic Dietary Assessment dated January 9, 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.

Tier I (screening level) EDWCs were calculated for streptomycin even though the active ingredient of most products is streptomycin sulfate. Streptomycin sulfate generally exists in the form of a salt powder, which has an ionic bond that disappears when dissolved in water producing streptomycin and sulfate ions; thus, the drinking water modeling conducted for streptomycin provides a valid prediction for the pesticide streptomycin sulfate.

Table 3 presents estimates for surface water (acute “peak” and chronic/cancer values) and groundwater based on aerial applications of streptomycin to apples.

Table 3. Highest surface/ground water EDWCs for streptomycin[1]

Crop	Spray Type	Chronic Surface Water EDWC	Chronic Ground Water EDWC
Apples	Aerial	51.4 ppb	1.2 ppb

[1] Streptomycin is the dissociation product of the pesticide a.i. streptomycin sulfate

Concentrations in surface water (51.4 ppb) and ground water (1.2 ppb) represent upper-bound estimates of the concentrations that might be found in surface water and ground water due to the use of streptomycin on apples. These drinking water exposure estimates were 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 Streptomycin Chronic Dietary Assessment dated January 9, 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 streptomycin.

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. In addition, FDA has established tolerances for residues of streptomycin in uncooked, edible tissues of chickens, swine, and calves of 2.0 ppm in kidney and 0.5 ppm in other tissues as listed in 21CFR Part 556.610. Accordingly, streptomycin residues in animals were also considered for inclusion in this assessment. However, 2002 USDA Food Safety and Inspection Service (USDA FSIS) National Residue Data reported no streptomycin residues in/on all livestock animals tested (2 to 634 animals in each production class). Therefore, EPA considered livestock commodities to have zero residues of streptomycin.

The chronic dietary assessments assumed tolerance level residues on treated crops and incorporated percent crop treated information. EDWCs from modeled values for either surface or ground water sources were also included. The chronic dietary exposure estimates for food and water are below EPA's level of concern. The highest exposure and risk estimates were for all infants (<1 year old) using surface water as the drinking water source and children 1 to 2 years old using ground water as the drinking water source. The exposure for all infants utilized 9.0% of the cPAD and the exposure for children 1 to 2 years old utilized 4.9% 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 for Streptomycin

	Surface Water			**Ground Water**		
Population Subgroup	**EDWC (ppb)**	**Total (Food + Water) Exposure (mg/kg/day)**	**% cPAD**	**EDWC (ppb)**	**Total (Food + Water) Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	51.4	0.001980	4.0	1.2	0.000922	1.8
All Infants (< 1 year old)	51.4	0.004479	9.0	1.2	0.001010	2.0
Children 1-2 years old	51.4	0.004021	8.0	1.2	0.002449	4.9

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

Residential Risk

(For a complete discussion, see the Streptomycin HED Chapter dated February 7, 2006.)

At this time, products containing streptomycin are registered for residential use on home garden orchards (apples and pears), and ornamentals (pyracantha, chrysanthemums, dieffenbachia, philodendron, and roses). Dermal and inhalation exposure to residential handlers can occur when they mix, load, or apply streptomycin for use in a sprayer.

Oral absorption of chemicals related to streptomycin is less than 1% because of the charged nature of the molecules. Because the skin has a protective barrier role in comparison to the lining of the gastrointestinal tract, dermal absorption is expected be much less than that by the oral route. Although a dermal exposure study is not available for streptomycin, dermal absorption at environmental concentrations is expected to be so minimal that toxicity by the dermal route is not of concern. Therefore, quantification of risk following dermal exposure is not required at this time.

A chronic inhalation exposure assessment was conducted for homeowner application to fruit trees and shrubs using a low pressure handwand. The resulting margin of exposure (MOE) is 75,000. MOEs (calculated as NOAEL ÷ dose) greater than 100 do not exceed EPA's level of concern; because the MOE for this use is greater than 100, risk from residential inhalation exposure does not exceed EPA's level of concern. The inhalation exposure assessment is considered a reasonable worst-case scenario for homeowners because streptomycin is poorly absorbed by the oral and dermal routes; therefore, a postapplication dermal and oral exposure assessment was not conducted.

Aggregate Risk

(For a complete discussion, see section the Streptomycin HED Chapter dated February 7, 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. 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 streptomycin, an aggregate assessment was performed using high-end exposures and conservative endpoints. No exposures of concern were identified. Since the screening level aggregate assessment did not show risks of concern, EPA concludes with reasonable certainty that combined residues of streptomycin from food, drinking water and residential 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 streptomycin could not be identified.

A chronic aggregate assessment for food, water, and residential exposure was conducted because a chronic toxicological endpoint was identified for streptomycin. Streptomycin residues in livestock animals resulting from FDA-approved uses were also considered for inclusion in this assessment. Livestock residues did not impact the aggregate assessment since the USDA FSIS National Residue Data reported no streptomycin residues in/on all livestock animals tested. The highest exposure and risk estimates for food and water were for all infants using surface water as a drinking water source, and children 1 to 2 years old using ground water as the drinking water source. The food and water exposure for all infants was 0.004479 mg/kg/day, which utilized 9.0% of the cPAD; and the food and water exposure for children 1 to 2 years old was 0.002449 mg/kg/day, which utilizes 4.9% of the cPAD. Even though chronic exposure from uses of streptomycin in residential settings is unlikely, as a worst-case scenario EPA aggregated the residential inhalation exposure of 0.000067 mg/kg/day with the food and water exposure for the General U.S. Population of 0.001980 mg/kg/day. The combined inhalation and dietary exposure is below EPA's level of concern. Results of the dietary (food + drinking water) exposure and risk assessment are presented in Table 4.

Intermediate-term aggregate risk estimates were not calculated because no intermediate-term residential exposures are expected.

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 streptomycin 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 streptomycin to FDA in a letter dated May 24, 2006, which is available in the public docket (EPA-HQ-OPP-2005-0493).

The pesticidal exposure estimates described in the May 24, 2006 letter reflect the dietary dose from pesticidal uses of streptomycin that a user treated with a pharmaceutical streptomycin 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 streptomycin.

EPA estimates that the pharmaceutical streptomycin exposure a user is expected to receive from a typical therapeutic dose (15 mg/kg/day) is 3,000 to 21,000 times greater than the estimated dietary exposure from the pesticidal sources of streptomycin (0.000704 mg/kg/day to 0.004479 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 streptomycin. FDA is aware of EPA's conclusions regarding pesticide exposure in users receiving treatment with a pharmaceutical streptomycin 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 streptomycin and any other substances, and streptomycin 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 streptomycin 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 streptomycin are established under 40 CFR 180.245. A summary of the streptomycin tolerance reassessment is presented in Table 5. FDA tolerances established in 21 CFR Part 556.610 are

Table 5. Tolerance Reassessment Summary for Streptomycin

Commodity	Current Tolerance (ppm)	Reassessed Tolerance (ppm)	Comments
Tolerances Under 40 CFR §180.245(a)(1)			
Pome, fruit	0.25	0.25	
Tolerances To Be Proposed Under 40 CFR §180.245(a)(1)			
Bean, dry	None	0.5	EPA has adequate data to support dry beans.
Bean, succulent	None	0.5	EPA has adequate data to support succulent beans.
Tolerances Under 40 CFR §180.245(a)(2)			
Celery	0.25	0.25	
Pepper	0.25	0.25	
Tomato	0.25	0.25	
Tolerances Under 40 CFR §180.245(a)(3)			
Potato	0.25	0.25	

FDA has established tolerances for residues of streptomycin in uncooked, edible tissues of chickens, swine, and calves of 2.0 ppm in kidney and 0.5 ppm in other tissues as listed in 21CFR Part 556.610. 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 Streptomycin HED Chapter dated February 7, 2006.)

Bacterial resistance to streptomycin as a result of drug use has long been recognized. EPA recognizes that pesticidal uses of streptomycin 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 0.001980 mg/kg/day for the General U.S. Population), it is unlikely that antibiotic resistance from pesticidal use of streptomycin would result from food exposure. Bacterial resistance to streptomycin from pesticidal use of streptomycin 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 streptomycin is unlikely to result directly from dietary residues of streptomycin because dietary residues are very low. The maximum aggregate dietary exposure is 0.004479 mg/kg/day which is very small when compared to a 15 mg/kg/day drug dose. The drug dose is 3,000 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 streptomycin 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 streptomycin. 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 streptomycin.

Additional Generic Data Requirements

Toxicity for streptomycin was assessed using the extensive database for streptomycin from its use as a human drug and using animal toxicity studies submitted to FDA. Toxicological and environmental fate data requirements were waived for streptomycin in the 1992 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 streptomycin in the environment and to support the continued registration of streptomycin.

Table 6. Streptomycin Generic Data Requirements

Guideline	Study Title
810.1000	Use and Usage Information
810.1000	Antibiotic Resistance in Orchards[1]
835.1230	Sediment and soil adsorption/desorption for parent and Degradates
835.2130	Hydrolysis as a Function of pH and Temperature

Guideline	Study Title
835.2210	Direct Photolysis Rate in Water by Sunlight
835.4100	Aerobic Soil Metabolism

[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 streptomycin.

Table 7. Streptomycin Label Changes Summary Table

Description	Amended Labeling Language	Placement on Label
General Application Restrictions	"This product contains the antibiotic streptomycin. 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 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 chronic exposure to streptomycin 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 streptomycin 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 streptomycin.

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 Streptomycin TRED

1. Kit Farwell (USEPA/OPPTS/OPP/HED). STREPTOMYCIN SULFATE (006310) and STREPTOMYCIN (006306), HED Chapter of the Tolerance Reassessment Eligibility Document (TRED), Revised After Phase 1 Error-Only Corrections. DP Barcode D310386. February 7, 2006.

2. Subijoy Dutta (USEPA/OPPTS/OPP/EFED). Tier I Estimated Drinking Water Concentrations of Streptomycin and Streptomycin Sulfate for use in the Human Health Risk Assessment as part of the Tolerance Reregistration Eligibility Decision (TRED). DP Bar Code D310392. November 30, 2005.

3. Toiya Goodlow (USEPA/OPPTS/OPP/HED). Streptomycin/Streptomycin Sulfate: Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED). DP Barcode D310391. January 9, 2006.

4. Monica S. Hawkins (USEPA/OPPTS/OPP/HED). Review of Streptomycin Incident Reports. DP Barcode D310389. August 24, 2005.