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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: September 30, 2008

SUBJECT: Fenazaquin: HED Risk Assessment for Proposed Section 3 Non-food Uses on Christmas trees (plantations), Outdoor and Greenhouse-grown Ornamental Plants, Established Ornamental Landscapes (including interiorscapes and around residential premises), and on Non-bearing Fruit and Nut Trees.

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The Registration Division (RD) of OPP has requested that HED estimate the risk to human health from the proposed use of the miticide, fenazaquin on Christmas trees (plantations), outdoor and greenhouse-grown ornamental plants, established ornamental landscapes (including interiorscapes and around residential premises), and on non-bearing fruit and nut trees. An assessment of human risk resulting from these proposed uses of fenazaquin is provided in this document. A risk assessment has already been completed for food-only dietary exposure to fenazaquin from residues on imported apples, pears and citrus fruits (D325204, J. Arthur, 05/15/07). This current assessment is for non-food uses, however, because it covers the first

proposed uses of fenazaquin in the U.S., it must take into account worker exposures, as well as the potential for residential and drinking water exposures, the latter of which must be aggregated with existing imported food-use dietary exposures. In order to avoid repetition of data and information, the previous assessment should be referred to for much of the residue chemistry, dietary (food only) and toxicology background discussion. This current assessment contains new information on worker risks, new toxicity endpoints for dermal and inhalation exposure and potential drinking water exposures resulting from the proposed new uses.

The hazard assessment, including proposed new dermal and inhalation points of departure, was provided by Whang Phang of RAB3, the occupational/residential risk assessment by Kelly O'Rourke of RAB3, the dietary risk assessment by Tina Moore on detail from the Office of Water, and the risk assessment by Jack Arthur of RAB3.

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1.0 EXECUTIVE SUMMARY

HED is conducting a risk assessment for the proposed use of the miticide, fenazaquin on Christmas trees (plantations), outdoor and greenhouse-grown ornamental plants, established ornamental landscapes (including interiorscapes and around residential premises), and on non-bearing fruit and nut trees. This represents the first fenazaquin use proposed for the United States.

Fenazaquin, 4-*tert*-butylphenethyl quinazolin-4-yl ether, is a quinazoline class insecticide/acaricide used primarily for the control of mites. It is approved for use on a variety of field, vegetable and fruit crops in a number of countries. Recently HED has evaluated and recommended approval of tolerances to support the use of fenazaquin on apples, pears and citrus fruits grown in other countries for export to the U.S. Specifically, the following permanent import tolerances for fenazaquin residues per se were established under 40 CFR 180.632:

Apple	0.2 ppm
Pear	0.2 ppm
Fruit, Citrus Group 10, except grapefruit	0.5 ppm
Citrus, Oil	10.0 ppm

For the current proposed non-food use on ornamentals, fenazaquin is formulated by Gowan as an 18.79% suspension concentrate to be applied using ground or hand-held equipment as a single foliar application at a rate of 0.15 to 0.3 lb active ingredient (ai) per acre.

Hazard Assessment

Fenazaquin is a miticide that exhibits both contact and ovicidal activity against a broad spectrum of mite and certain insects through inhibition of mitochondrial electron transport at the Complex I. The toxicology database is considered adequate for an import food tolerance. Fenazaquin is acutely toxic (Toxicity Category II) when administered orally in rats (LD50 = 134/138 mg/kg in males/females). Toxicity is low with acute dermal and inhalation exposures. While not a skin irritant, skin sensitization is assumed in lieu of an acceptable study. It is minimally irritating to the eye. Following repeated oral administration in 90-day and chronic toxicity studies using rats, hamsters, or dogs, the major findings were decreased body weight and gain in addition to reduced food intake and efficiency. Testicular atrophy and decreased prostate weight were additional findings in the 90-day hamster study seen at relatively higher doses (≥75 mg/kg/day) than those used in the 18-month hamster study (high dose = 30 mg/kg/day). Decreased body weight/weight gain and food intake/efficiency were also identified in parental animals of the rat developmental and reproduction studies and in the offspring of the reproduction rat study. There were no developmental findings in the rat study and no parental or developmental findings of any kind up to 60 mg/kg/day in the rabbit developmental study. There is no clear evidence of consistent neurotoxicity findings in the available toxicity studies. Excessive salivation was reported at the high dose in the rat two-generation reproduction toxicity study in addition to possibly decreased motor activity and impaired righting reflex in the preliminary reproduction study. There are no available acute or 90-day neurotoxicity studies but the findings in the reproduction studies are

unlikely to be a sign of neurotoxicity since the chemical is not known to have a neurotoxic mode of action and no similar clinical findings were reported in the 90-day or chronic/carcinogenicity studies at doses (up to 33 and 26 mg/kg/day, respectively) comparable to those used in the reproduction studies (25-27.5 mg/kg/day).

There were no indications of pre- or post-natal enhanced sensitivity or susceptibility to the young. The residual uncertainty due to inadequate dosing in the rabbit developmental study should not impact the current evaluation because acute and chronic dietary endpoints are based on a NOAEL of 10 mg/kg/day (maternal animals in the rat developmental study) and 5 mg/kg/day (parental animals of the reproduction study), respectively, which are well-below the high dose of 60 mg/kg/day in the rabbit developmental study.

Fenazaquin appears to increase peroxisomal proliferation in rats and mice but hamsters were resistant since peroxisomal beta oxidation was not increased in the 90-day hamster study. Oxidation of the t-butyl substituent (to the corresponding carboxylic acid) on the alkylbenzene moiety of fenazaquin appears to be the critical step for heptatocellular peroxisome proliferation in a female mouse study.

There were no findings of carcinogenicity in rat and hamster studies and no findings of mutagenicity in an *in vitro* and *in vivo* test battery.

At 168 hours following oral administration in rats, most of the radiolabeled fenazaquin (89.5-107.7%) was recovered in rat excreta with approximately 20% of the radiolabel in urine. Additional minor amounts were recovered in the carcass (0.5-1.6%) and tissues (<0.04% of the dose in each tissue). Based on characterization of excretable metabolites, fenazaquin may undergo oxidation to alcohol and/or carboxyolic acid derivatives; alternatively, the ether bond may be hydrolyzed to the respective alcohol and carboxylic acid fragments.

In conclusion, there is no evidence of developmental or reproductive toxicity, mutagenicity or carcinogenicity.

Dietary/Aggregate Risk Estimates

The conservative acute and chronic dietary risk assessments conducted with DEEM-FCID™ indicate that food and drinking water exposures to fenazaquin are well below HED's level of concern. They are unrefined utilizing the entire consumption distribution and a single upper-bound residue value for all included foods. The resulting assessment models for fenazaquin are reported at the 95th percentile of exposure for the general U.S. population and all of its subgroups. Subsequently, acute dietary exposure to fenazaquin was estimated to be 7% of the aPAD for the general U.S. population. In comparison, chronic dietary exposure to fenazaquin was estimated to be 3% of the cPAD for the general U.S. population. For the most highly exposed population subgroup, children 1-2 years of age, both acute and chronic dietary risk were estimated to be well below HED's level of concern. For this subgroup, the acute analysis was found to be only 24% of the aPAD and the resulting chronic determination just 13% of the cPAD. As a result, the risk estimates made with DEEM-FCID™ are adequate in supporting the tolerance levels established

for fenazaquin on imported apples, pears, and citrus fruits. In addition, through inclusion of potential fenzaquin residues in drinking water, the DEEM-FCID analyses support the requested uses of fenazaquin in/on non-food crops.

Residential Exposure/Risk

An emulsifiable concentrate liquid (GWN-1708) is intended for use by professional applicators to ornamental landscape plantings, including residential areas. While residues of fenazaquin may be present on the foliage after application, contact with the ornamentals by homeowners and their children is expected to be minimal. Therefore, residential exposure is expected to be negligible for this use and a residential exposure/risk assessment was not conducted.

Occupational Exposure/Risk

Short-term handler exposure is possible via the dermal and inhalation routes, and short-/intermediate-term postapplication dermal exposure may occur from the proposed uses.

No chemical-specific handler exposure data were submitted in support of these proposed Section 3 registration actions. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99).

The results of the occupational handler exposure and risk assessment indicate that most of the scenarios have MOEs above the LOC of 100 when gloves are added to baseline clothing (long-sleeve shirt, long pants, shoes and socks). To reach an MOE of 100, additional personal protective equipment (PPE) is necessary for mixing/loading/applying with a high-pressure handwand (gloves and coveralls). A dermal absorption or dermal toxicity study would be helpful in refining this scenario; the dermal MOE calculations are based on the conservative assumption of 100% dermal absorption.

Occupational postapplication risks were assessed for hand pruning, harvesting, and burlapping containerized ornamentals. The short- and intermediate-term dermal MOEs for occupational postapplication are greater than the LOC of 100 on the day of application (indicating a restricted entry interval [REI] of 12 hours); and therefore, are not of concern. The technical material has been classified in Toxicity Category IV for acute dermal and primary skin irritation, and Category III for primary eye irritation. Per the Worker Protection Standard (WPS), a 12-hr REI is required for chemicals classified under Toxicity Category III/IV. The proposed fenazaquin label specifies an REI of 12 hrs, which is in compliance with the WPS.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations." As a

part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical (PHED 1998). These studies have been determined to require a review of their ethical conduct, and some are also subject to review by the Human Studies Review Board. The studies used in this assessment have received appropriate review.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

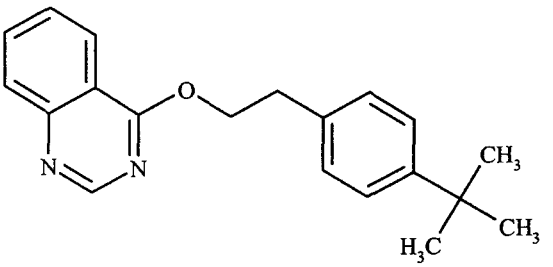
Currently, there are no registered uses of fenazaquin. U.S. tolerances have been extablished for residues of fenazaquin on imported apples, pears and citrus. The registrant, Gowan Company, has requested the registration of the product GWN-1708 (EPA Reg No. 10163-EOT), containing the insecticide fenazaquin, for the control of mites and whiteflies on Christmas trees (plantations), outdoor and greenhouse-grown ornamental plants, established ornamental landscapes (including interiorscapes and around residential premises), and on non-bearing fruit and nut trees. The use profile proposed for this Section 3 registration request is summarized in Table 1.

Table 1. Summary of Use Pattern/Formulation Information					
Formulation Type	**Application Method**	**Use Site**	**Application Rate**	**Application Interval**	**Preharvest Interval**
GWN-1708 (emulsifiable concentrate) 18.79% ai	Groundboom, Airblast, Low- and High-pressure Handheld Equipment [1]	**Non-Food**: Foliage crops, Christmas Tree Plantations, Non-bearing Fruit and Nut Trees, and Ornamental Plants	0.15 to 0.3 (lb ai/A)	N/A [2]	N/A

[1] Aerial applications are prohibited, and product is not to be applied through any type of irrigation system.
[2] Only one application per cropping is permitted (not to exceed 0.3 lb ai/A/yr for outdoor settings, or 0.6 lb ai/A for indoor settings).

2.2 Structure and Nomenclature

The structure and nomenclature of fenazaquin is presented below in Table 2.

Table 2. Fenazaquin Nomenclature.	
Compound	
Common name	Fenazaquin
Molecular weight	306.4
Company experimental names	XDE-436, EL-436, XRD-562;,DE-436
IUPAC name	4-*tert*-butylphenethyl quinazolin-4-yl ether
CAS name	4-[2-[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline
CAS registry number	120928-09-8
End-use products (EP)	100 g/L EC (MAGISTER® 100 EC) 200 g/L FlC (MAGISTER® 200 SC and MATADOR® 200 SC)

2.3. Physical and Chemical Properties

The physicochemical properties of fenazaquin are presented below in Table 3.

Table 3. Physicochemical Properties of Fenazaquin.					
Parameter	Value				Reference
Melting point/range	77.5-80°C				Evaluation on Fenazaquin, Issue No. 150, Pesticides Safety Directorate, Depart. for Environment, Food, and Rural Affairs, U.K., March 1996
pH	Not determined due to low solubility				
Relative Density	1.16 at 21°C				
Water solubility (20°C)	0.102 mg/L at pH 5 & 7 0.135 mg/L at pH 9				
Solvent solubility (g/L at 23°C)	acetonitrile n-chlorobutane dichloromethane dimethylformamide hexane methanol N-methyl-2-pyrrolidone	33-50 >500 >600 300-400 33-50 50-100 >500	acetone chloroform ethyl acetate ethylene glycol isopropanol toluene	400-500 >500 400-500 <5 50-100 >500	
Vapor pressure (25°C)	1.9×10^{-5} Pa				
Dissociation constant, pK_a	2.44				
Octanol/water partition coefficient, $Log(K_{OW})$	5.71 at 25°C; 5.51 at 20°C				
UV/visible absorption spectrum	Not available				

3.0 Hazard Characterization/Assessment

Also Ref: HED: "*Fenazaquin: PP# 9E5059. Tolerances on Apples, Pears and Citrus Fruits Exported to the US. HED Risk Assessment.*" Jack Arthur, (RAB3), Decision #: 302678, DP #: 325204, 05/15/07.

3.1 Hazard and Dose-Response Characterization

Fenazaquin is acutely toxic when administered orally in rats (Tox. Cat. II). With acute dermal and inhalation exposures, it produces low toxicity (Tox. Cat. IV and III, respectively). Fenazaquin is not a skin irritant, but is minimally irritating to the eye. Further, in lieu of an acceptable dermal sensitization study demonstrating otherwise, TRB/RD recommends this chemical be labeled as a dermal sensitizer

The major findings following repeated oral administration in rats, hamsters and dogs were non-specific effects characterized by decreases in body weight, body weight gain, food intake, and food efficiency. These severity of the effect does not seem to progress with time irrespective of the methods of administration (i.e.gavage or feeding). With one exception, these findings occurred at the highest tested dose ($\leq$ 35 mg/kg/day) in each of the subchronic or chronic toxicity studies. In the 90-day hamster study which used doses up to 150 (males) and 100 (females) mg/kg/day, the magnitude of the decrease was dose-dependent for body weight (8-23% and 19-28% in males and females, respectively) and body weight gain (16-74% and 39-61% in males and females, respectively); however, due to food spillage problems, food consumption and efficiency data were not presented. In the same study, testicular atrophy (dose-dependent decreased weight and hypospermatogenesis) and decreased prostate weight/relative weight were

also evident at 75 and 150 mg/kg/day. At the doses used (≤ 35 mg/kg/day) in all remaining subchronic and chronic toxicity studies, there were no organ specific toxicity findings. Similar effects on body weight/weight gain and food intake/efficiency were also identified in parental animals of the rat developmental and reproduction studies and in the offspring of the reproduction rat study. There were no developmental findings in the rat study (up to 40 mg/kg) and no parental or developmental findings of any kind up to 60 mg/kg/day in the rabbit developmental study.

There are no specific neurotoxicity studies, including acute-, subchronic-, or developmental. There is no clear evidence of consistent neurotoxicity findings in the available toxicity studies. Findings of excessive salivation in the rat reproduction toxicity study are unlikely to be a sign of neurotoxicity since the chemical is not known to have a neurotoxic mode of action and no similar clinical findings were reported in the 90-day or chronic/carcinogenicity studies.

Fenazaquin appears to increase peroxisomal proliferation in rats and mice but hamsters were resistant since peroxisomal beta oxidation was not increased in the 90-day hamster study.

A supplementary report (MRID 44742910) was provided as justification for using the hamster as an appropriate animal model for fenazaquin. Based on the report, the NOAEL in a three-month feeding study in mice was 150 mg/kg/day in males and > 600 mg/kg/day in females and the only effect observed was a decrease in body weight gain. (The actual 90-day mouse study was not made available to HED.) In the similar rat and hamster toxicity studies, the NOAEL was 10 and 25 mg/kg/day, respectively, based on decreased body weight gain (in addition to hamster testicular atrophy) thus showing that the rat and hamster were more sensitive to the effects of fenazaquin than mice. Additionally, a comparative pharmacokinetic analysis showed that peak plasma levels were not proportional to dose in both male and female mice, but area under the curve (AUC) was well correlated to dose. Peak plasma levels were observed between 0.5-4 hours post dosing. Plasma elimination rate of fenazaquin was dose dependent and became slower at doses ≥300 mg/kg. Conversely, rat peak plasma level was reached in 8 hours and AUC was proportional to dose while elimination was independent of dose. Results from the pharmacokinetics study indicated similar pharmacokinetics of radiolabeled fenazaquin in the hamster at doses between 5 and 125 mg/kg with peak plasma levels being reached in 2 hours.

The hamster was chosen over the mouse for a second carcinogenicity study based on findings in the hamster of slower elimination kinetics and greater systemic toxicity. Because of the high tolerance of the mouse in regard to effect on body weight gain, the laboratory chose to use Syrian golden hamsters as a secondary rodent model, along with rats. The results of both rat and hamster carcinogenicity studies indicate that fenazaquin at doses tested does not present evidence of carcinogenicity. The in-vitro and in-vivo test battery demonstrate negative mutagenic results.

3.1.1 Database Summary/Sufficiency of Toxicity Data

The database of available toxicity studies is adequate for selecting endpoints for the acute and chronic dietary reference doses and for dermal and inhalation exposure assessments for workers. However, there are no acute and subchronic neurotoxicity screening studies, subchronic dermal

toxicity study, and immunotoxicity study. These studies are required with the proposed uses and under the current guidelines (Federal Register/Vol.72, No. 207; Oct. 26, 2007. §158.500).

HED has considered the entire fenazaquin toxicity data base for potential neurotoxic and immunotoxic effects. Although there are uncertainties in the absence of the required acute and subchronic neurotoxicity and immunotoxicity studies, HED does not believe it necessary to assign a UF_{db} for the lack of these data based on the following: 1) the NOAEL used for the acute dietary risk assessment is protective of the clinical signs indicative of neurotoxicity in the acute oral study [see "Comments about Study/Toxicity Endpoint/Uncertainty Factor" in Section 3.2.1] and 2) based on the toxicity profile of this chemical, it is unlikely that the results of an immunotoxicity study would result in a NOAEL lower than that of 5 mg/kg/day used for chronic, dermal and inhalation risk assessments. The NOAELs/LOAELs (5/25 mg/kg/day) in the two-generation reproduction study is also similar to the NOAEL/LOAEL in the studies with rats, dogs, and hamsters (9.2/18.3, 5/12, and 2/15 mg/kg/day, respectively).

3.1.1.1 Studies available and considered (animal, human, general literature)

- Subchronic: Dietary 90-day toxicity (rat); gavage 90-day toxicity (rat), 90-day oral toxicity (hamster), 6-month oral toxicity (dog)
- Developmental: rat and rabbit developmental toxicity studies
- Reproduction: 2-generation reproduction study (rat)
- Chronic: combined oral chronic toxicity/carcinogenicity (rat); oral carcinogenicity (hamster); 1-year oral toxicity (dog)
- Other: mutagenicity battery
- Metabolism study
- Liver hypertrophy and peroxisomal acyl-CoA oxidase activity (mouse)

3.1.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Fenazaquin is a miticide that exhibits both contact and ovicidal activity against a broad spectrum of mite and certain insects by inhibiting mitochondrial electron transport at the Complex I site (NADH-ubiquinone reductase).

Metabolism studies were conducted in Fischer 344 rats of both sexes by gavage administration of uniformly labeled fenazaquin on either the t-butyl-phenyl ring or the quinazoline-phenyl ring at a single dose (1 or 30 mg/kg) or 14-daily doses (1 mg/kg/day).

Irrespective of the dosing regimen, most of the radioactivity was recovered in excreta (89.5-107.7%) at 168 hours post dosing with approximately 20% of the radiolabel in urine and the remainder in feces. Initially, fenazaquin was uniformly distributed in rat tissues but the levels were very low at the end of the study being about 0.5-1.6% of the dose in the carcass and below 0.04% of the dose in each tissue. There was no radiolabel in the expired air and no evidence for bioaccumulation.

It is not possible to accurately determine the extent of systemic absorption or bioavailability of fenazaquin because no study is available on bile cannulation or intravenous administration. Based on excretion (recovery in urine) and tissue residue data, systemic absorption is estimated at about 20% which is likely to be higher because some of the nearly 80 % fecal radioactivity may be excreted through bile following systemic absorption. An additional bile cannulation study in rats using a low dose is recommended to help determine systemic absorption of fenazaquin.

Non-metabolized fenazaquin was higher in feces (1.0-15.0% of administered dose) than in urine (below 0.5% of dose) and some of the major metabolites were identified including AN-1 (4.2-5.8% of dose) in urine in addition to the fecal metabolites F-1, F-2 and F3 representing 3.5-8.4%, 11.9-19.9%, and 4.7-10.5% of the dose, respectively. The metabolic pathway of fenazaquin involved cleavage of the ether bond, resulting in the formation of the respective alcohol (4-OH quinazoline metabolite) and carboxyl acid (AN-1) derivatives. Other biotransformation reactions included oxidation of one of the methyl groups on the alkyl side chain to produce either an alcohol (F-1) or carboxylic acid (F-2) metabolites. Finally, hydroxylation at the O-ether alkyl moiety of the metabolite F-1 or at the 2-position of the quinazoline ring of the metabolite F-2 revealed the formation of F-1A and F-3 metabolites, respectively.

Fenazaquin and several of its analogs (with varying susceptibilities to metabolism of the ether bond or the alkylbenzene substituents) were assessed for their peroxisomal proliferation potential in groups of five CD-1 female mice on day five following four daily gavage administrations at equimolar concentrations. Fenazaquin dose-dependently increased mouse liver peroxisomal fatty acyl-CoA oxidase (FAO, a marker of peroxisomal proliferation) and relative liver weight at doses from 100 to 750 mg/kg/day. Based on FAO activity data, oxidation of the t-butyl substitutent on the alkylbenzene moiety (in fenazaquin or analogues) appears to be the critical step for hepatocellular peroxisome proliferation in mice. Analogs of fenazaquin with an alkylbenzene substitutent that can be oxidized to a carboxylic acid were active peroxisome proliferators while analogs less susceptible to oxidation (e.g., OCF_3 instead of t-butyl) were inactive. Hydrolysis and subsequent oxidation of the ether bond of fenazaquin and its analogs did not result in pronounced induction of peroxisome proliferation. In addition, halogenation of the quinazoline moiety increased toxicity of the compounds with no significant increase in liver weight or FAO activity. In conclusion, the FAO peroxisomal activity data indicate that oxidation of the t-butyl substituent on the alkylbenzene moiety (to the corresponding carboxylic acid) of fenazaquin and related compounds appears to be the critical step for heptatocellular peroxisome proliferation in female CD-1 mice.

3.1.2 **FQPA Safety Factor** (The details for FQPA Consideration are presented in Section 3.3)

Based on the hazard and exposure data, the fenazaquin risk assessment team has recommended that the FQPA Safety Factor be reduced to 1x because: (1) the toxicity database is sufficient for selecting toxicity endpoints for assessing risk for the proposed uses of fenazaquin on ornamental plants; (2) exposure data are complete or are estimated based on data that reasonably account for potential exposures; (3) there is no evidence of susceptibility following *in utero* and/or postnatal exposure in the developmental toxicity studies in rats or rabbits, and in the two-generation rat

reproduction study; (4) there are no residual uncertainties concerning pre- and postnatal toxicity; and (5) the dietary food exposure assessment utilizes tolerance level or higher residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated. The uncertainty factors for this risk assessment are 10x for interspecies extrapolation and 10x for intraspecies variability.

3.2 Hazard Identification and Toxicity Endpoint Selection

The toxicity endpoints and the points of departures for risk assessment were selected based on analysis of all the available toxicity data and are summarized in Table 4. The rationale for the selections of the acute and chronic reference doses and the new short- and intermediate-term dermal and inhalation points of departure for workers are summarized below.

3.2.1 Acute Reference Dose (aRfD) – All Populations

Study Selected: developmental toxicity study - rat (Guideline §870.3700a)
MRID No.: 45029911

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45029911) EL-436 (Fenazaquin; 98% a.i., Lot ACD13041) was administered to 25 mated female CD [Crl:CD®(SD)] rats/dose by gavage in 10% (w/v) aqueous acacia solution at dose levels of 0, 3, 10, or 40 mg/kg bw/day on gestation days (GDs) 6 through 17. On GD 20, dams were sacrificed and necropsied. Gravid uterine weights, corpora lutea counts, and the numbers and positions of implantations, live and dead fetuses, and early and late resorptions were recorded. All fetuses were weighed, sexed, and examined for external anomalies. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination.
There were no deaths, abortions, or treatment-related clinical signs or gross pathological findings. At the 40 mg/kg bw/day dose level, mean body weight gain was markedly decreased throughout treatment (62%, 26%, and 12% less than controls during GDs 6-9, 10-13, and 14-17, respectively; $p<0.05$), and a compensatory increase was seen during GD 18-19 (+26%; $p<0.05$). These changes corresponded to decreased food consumption by this group throughout treatment (9-15% less than controls; $p<0.05$), with subsequent increased food consumption during GD 18-19 (+10%; $p<0.05$).

The Maternal Toxicity LOAEL for Fenazaquin in CD rats is 40 mg/kg bw/day, based on decreased food consumption and decreased body weight gain. The Maternal Toxicity NOAEL is 10 mg/kg bw/day.

There were no treatment-related increases in fetal deaths/resorptions, and there were no treatment-related effects on fetal sex ratios, fetal body weight, or the incidences of fetal runts. There was no evidence of altered fetal ossification rates. Malformations were observed in 1/24, 3/25, 1/22, and 1/23 litters from the control, low-, mid-, and high-dose groups, respectively, and there were no significant increases in litter or fetal incidences of any individual structural abnormalities for any treated group.

The Developmental Toxicity LOAEL for Fenazaquin in CD rats is greater than 40 mg/kg bw/day, and the Developmental Toxicity NOAEL is equal to or greater than 40 mg/kg bw/day.

This developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a rat developmental toxicity study (OPPTS 870.3700; OECD 414).

Dose and Endpoint for Risk Assessment: Maternal NOAEL = 10 mg/kg/day, based on decreased body weight gain, food intake, and food efficiency as early as gestation day 6-9 at the LOAEL of 40 mg/kg/day. These findings in the high dose group were clearly related to treatment and were statistically significantly (SS) different compared to the findings in control animals. Dosing administration commenced on gestation day (GD) 6 and, at the first measurement on GD 9, body weight gain and food intake were SS reduced by 62% and 15% respectively. During the same period, food efficiency was also decreased from 30.8 % to 13.6%. All three parameters were below respective control values during the remainder of the treatment period but rebounded (i.e., increased relative to control) after cessation of treatment (days 18 and 19).

Comments about Study/Endpoint/Uncertainty Factor: The endpoint could occur following one oral dose and is therefore appropriate for acute dietary risk assessment. The findings in the rat developmental study are supported by information on clinical signs and body weight in the available rat acute oral toxicity study (LD_{50}). In the acute oral toxicity study (MRID 46684003), surviving rats of both sexes had some or all of the following clinical signs of toxicity: hypoactivity, ataxia, diarrhea or soft stool, low carriage, hunched posture, soiling, hind-limb paralysis or weakness, and piloerection. (In the acute toxicity study, the lowest dose tested in males and females was 100 and 50 mg/kg, respectively.) The signs occurred within 1 or 2 hours and lasted up to 2 or more days in the surviving animals at all the tested doses from 50 to 300 mg/kg/day with some dose-dependency regarding which signs were seen. At its earliest measurement on day 8 post-dosing, body weight gain was also reduced by 20% in the surviving 100 mg/kg dose males and by 54%, and 7% in the surviving females at 100 and 50 mg/kg, respectively. In conclusion, the findings of clinical signs and decreased body weight following a single oral dose of 50 mg/kg or higher support the findings in the rat developmental study and the end-point (NOAEL/LOAEL = 10/40 mg/kg) that were selected for acute dietary risk assessment.

3.2.2 Chronic Reference Dose (cRfD)

Study Selected: 2-generation reproduction toxicity study - rat (Guideline §870.3800)
MRID No.: 46684001
EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 46684001), EL-436 (fenazaquin, 98.4% a.i., lot # 241MH8) was administered daily by gavage to 30 male and 30 female Crl:CD® (SD)BR rats/group at doses of 0, 1, 5, or 25 mg/kg/day. An additional 10 F_1 males and females/group were maintained on study during premating, but were sacrificed prior to breeding. One litter was produced in each generation. F_0 and F_1 parental males were administered the vehicle (aqueous 10% acacia) or test article for at least 70 days prior to mating and during cohabitation; F_0 and F_1 parental females were administered vehicle or test article for 70 days prior to mating and throughout mating, gestation, and lactation.

Deaths of several treated and control animals from both generations were considered incidental to test article administration. During premating, the incidence of excessive salivation in the high-dose groups was 20/30 F_0 males, 14/30 F_0 females, 21/40 F_1 males, and 16/40 F_1 females (all $p \leq 0.01$). This finding was not seen in control animals and occurred at low incidence in the low- and mid-dose groups (0-7 animals/group). The incidence of excessive salivation was also significantly increased in high-dose females of both generations during gestation and in high-dose F_0 females during lactation.

During the first week of premating, body weight gain by the high-dose F_0 males was significantly less ($p \leq 0.01$; 7% decrease) than that of the controls and corresponded with significantly ($p \leq 0.05$; 4% decrease) lower food consumption for that week. Absolute body weight for the high-dose F_0 males was slightly less than the controls throughout the study, although statistical significance was not attained. Body weight, body weight gain, and food consumption by all groups of treated F_0 females were similar to those of the controls during the premating interval.

Body weight of the high-dose F_1 males and females was significantly less ($p \leq 0.05$ or 0.01) than that of controls through premating day 43 for males (↓4-10%) and day 64 for females (↓4-7%). For the remainder of premating, body weight was similar to the control level. The only effect on body weight gain was during the first week of premating when weight gain by the high-dose animals was decreased by 12% for males and 9% for females (both $p \leq 0.01$). Thereafter, weight gain by the treated groups during premating was occasionally slightly greater than or less than that of the controls. Food consumption by the high-dose F_1 males and females was significantly less ($p \leq 0.01$; ↓7-8%) during the second week of treatment; no other effects on food consumption were seen. Body weight, body weight gain, and food consumption by the low- and mid-dose F_0 males and F_1 males and females were similar to those of the controls during the premating interval.

Body weight, body weight gain, and food consumption were similar between the treated and control F_0 and F_1 females during gestation and the F_1 females during lactation. High-dose F_0 females had significantly greater ($p \leq 0.01$; ↑5%) absolute body weight on lactation day 21 compared with the controls. Correspondingly, body weight gain by the high-dose F_0 females was significantly greater than that of the controls during lactation. Food consumption by the high-dose F_0 females was not affected by treatment during lactation.

Testes weight was not affected by treatment. Gross necropsy was unremarkable and no treatment-related microscopic lesions were found in tissues from the reproductive tract of males or females of either generation.

The Parental Systemic Toxicity LOAEL for EL-436 in male and female Crl:CD® (SD)BR rats is 25 mg/kg bw/day based on clinical signs of toxicity and transient decreases in body weight, weight gain, and food consumption. The Parental Systemic Toxicity NOAEL is 5 mg/kg bw/day.

No dose- or treatment-related differences in number of litters, number of pups/litter, pup survival, or pup sex ratio were observed between the treated and control groups of either generation. No treatment-related clinical signs of toxicity were seen in the pups during lactation.

No statistically significant differences in absolute body weight were seen between offspring in the treated and control groups of either generation. Pup body weight data were not separated by sex. Weight gain by the pups in the high-dose group of both generations was decreased by 11-13% during lactation days 4-7 with no compensation evident during the remainder of lactation. This lower weight gain is considered treatment-related and is the likely reason absolute body weight of the high-dose F_1 animals was less than that of the controls during the early phase of premating.

The Offspring/Developmental Toxicity LOAEL for EL-436 in male and female Crl:CD® (SD)BR rats is 25 mg/kg/day based on reduced body weight gain during lactation days 4-7. The Offspring/Developmental Toxicity NOAEL is 5 mg/kg bw/day.

No treatment-related differences in pre-coital interval, number of pregnant females, gestation length, or number of whole litter losses were seen between the treated and control groups of either generation during litter production. Estrous cyclicity and sperm parameters were not evaluated.

The Reproductive Toxicity NOAEL for EL-436 in male and female Crl:CD® (SD)BR rats is greater than or equal to 25 mg/kg bw/day and the Reproductive Toxicity LOAEL is greater than 25 mg/kg/day.

Dose and Endpoint for Risk Assessment: Parental systemic toxicity NOAEL = 5 mg/kg/day, based on decreased body weight/weight gain, and food intake in addition to increased salivation at the LOAEL of 25 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor: The same endpoint based on decreased body weight/weight gain, and food intake is found in other repeated-dosing oral studies with fenazaquin (by dietary feeding or via gavage) in all tested species and is therefore appropriate for chronic dietary risk assessment. The NOAEL/LOAEL (5/25 mg/kg/day) in the two-generation reproduction study is also similar to the NOAEL/LOAEL in the chronic toxicity (or carcinogenicity) studies in rats, dogs, and hamsters (9.2/18.3, 5/12, and 2/15 mg/kg/day, respectively).

3.2.3 Short-Term Dermal and Inhalation Exposures

Study Selected: Prenatal Developmental Toxicity Study – Rat
(Guideline §870.3700a) (MRID 45029911)

EXECUTIVE SUMMARY: In a developmental toxicity study, EL-436 (Fenazaquin; 98% a.i., Lot ACD13041) was administered to 25 mated female CD [Crl:CD®(SD)] rats/dose by gavage in 10% (w/v) aqueous acacia solution at dose levels of 0, 3, 10, or 40 mg/kg bw/day on gestation days (GDs) 6 through 17. On GD 20, dams were sacrificed and necropsied. There were no deaths, abortions, or treatment-related clinical signs or gross pathological findings. At the 40 mg/kg bw/day dose level, mean body weight gain was markedly decreased throughout treatment (62%, 26%, and 12% less than controls during GDs 6-9, 10-13, and 14-17, respectively; $p<0.05$),

and a compensatory increase was seen during GD 18-19 (+26%; $p<0.05$). These changes corresponded to decreased food consumption by this group throughout treatment (9-15% less than controls; $p<0.05$), with subsequent increased food consumption during GD 18-19 (+10%; $p<0.05$).

The Maternal Toxicity LOAEL for Fenazaquin in CD rats is 40 mg/kg bw/day, based on decreased food consumption and decreased body weight gain. The Maternal Toxicity NOAEL is 10 mg/kg bw/day.

There were no treatment-related increases in fetal deaths/resorptions, and there were no treatment-related effects on fetal sex ratios, fetal body weight, or the incidences of fetal runts. There was no evidence of altered fetal ossification rates. Malformations were observed in 1/24, 3/25, 1/22, and 1/23 litters from the control, low-, mid-, and high-dose groups, respectively, and there were no significant increases in litter or fetal incidences of any individual structural abnormalities for any treated group.

The Developmental Toxicity LOAEL for Fenazaquin in CD rats is greater than 40 mg/kg bw/day, and the Developmental Toxicity NOAEL is equal to or greater than 40 mg/kg bw/day.

Dose and Endpoint for Risk Assessment: Maternal NOAEL = 10 mg/kg/day based on the decreased body weight gains, food consumption, and food efficiency found in maternal LOAEL of 40 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor: The toxicity endpoint selected is most relevant in terms of duration of exposure and effects seen among all the appropriate studies.

3.2.4 Intermediate-Term Dermal and Inhalation Exposures

Study Selected: 90-Day Oral Toxicity – Dog (780.3150)
(MRID 45029901)

EXECUTIVE SUMMARY: In a 90-day oral toxicity study, fenazaquin (98.1% a.i., lot# 435MH8) was administered to 4 Beagle dogs/sex/dose in diet at dose levels of 0, 1, 5, or 15 mg/kg bw/day. For beagle dogs, no toxicological effects on organ weight, clinical chemistry, clinical signs, hematology, gross and histopathology were related to dietary exposure to fenazaquin. At 15 mg/kg/day dose, significant reductions in body weight of males (6 to 12%) and females (4 to 11%) were reported. At the high dose, overall body weight gain decreased in males (76%) and females (73%); mean food consumption was reduced in males (6 to 24%) and females (10 to 27%). Food efficiency values were also significantly decreased in high dose groups, males (72%) and females (67%). These specific body weight and food consumption effects have been similarly reported in the chronic 1-year dog study of fenazaquin dietary exposure with the same percentage of reduction in the first 90 days. Based on reductions of body weight, body weight gain, food consumption and food efficiency; the LOAEL is established at 15 mg/kg/day. NOAEL is 5 mg/kg/day.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on the decreased body weight, body weight gains, food consumption, and food efficiency seen at the LOAEL of 15 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor: The selected toxicity endpoint is supported by the results of the repeated dosing studies in rats (subchronic, chronic, and reproduction studies) and dogs. The data indicate no species and duration of exposure differences in response to the fenazaquin's effect on body weight and food consumption as illustrated by the established NOAELs/LOAEL s in reproduction or chronic toxicity studies in rats, dogs, and hamsters (5/25, 9.2/18.3, 5/12, and 2/15 mg/kg/day, respectively).

3.2.5 Summary of Toxicological Doses and Endpoints

Ref: : *Fenazaquin: ToxSAC meeting on August 7, 2008.* DP#: 328334. Jessica Kidwell, Executive Secretary ToxSAC. 08/13/08.

Table 4 presents a summary of the endpoints selected for fenazaquin by the RAB3 risk assessment team and confirmed by HED's Science Advisory Council for Toxicity. A summary of the acute toxicity categories for the technical material are included in Table 5.

Table 4 Summary of Toxicological Doses and Endpoints for Fenazaquin for Use in Dietary and Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All Populations, including Females 13-49 and Infants/Children)	NOAEL= 10 mg/kg/day	UF_A= 10 x UF_H= 10 x FQPA SF= 1 x	Acute RfD = 0.1 mg/kg/day aPAD = 0.1 mg/kg/day	Rat developmental toxicity LOAEL = 40 mg/kg/day based on findings (as early as GD 6-9) of decreased body weight gain, food intake, and food efficiency. The acute effects of fenazaquin was demonstrated in acute oral toxicity study where at 50 mg/kg/day, the test animals showed clinical signs including hunched posture, straub tail, hypoactivity, and soft stools.
Chronic Dietary (All Populations)	NOAEL= 5 mg/kg/day	UF_A= 10 x UF_H= 10 x FQPA SF= 1 x	Chronic RfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	Rat two-generation toxicity study LOAEL = 25 mg/kg/day based on excessive salivation and decreased body weight/weight gain and food intake.
Short-term Dermal and Inhalation , (1-30 days	Maternal NOAEL=10 mg/kg/day	UF_A= 10 x UF_H= 10 x FQPA SF= 1 x	LOC for MOE =100	Rat developmental toxicity Maternal LOAEL = 40 mg/kg/day based on decreased body weight gain, food intake, and food efficiency.
Intermediate-Term Dermal and Inhalation (1-6 months)	NOAEL 5 mg/kg/day	UF_A= 10 x UF_H= 10 x FQPA SF= 1 x	LOC for MOE =100	90-day feeding study in dogs LOAEL=15 mg/kg/day based on decreased body weight, body weight gains, food consumption and efficiency. Similar effects were seen in 90-day and chronic feeding study in rats with comparable LOAELs.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. LOC = level of concern. MOE = margin of exposure. Dermal absorption factor: 100%.

Table 5. Acute Toxicity of Fenazaquin Technical				
Guideline No.	**Study Type**	**MRID#**	**Results**	**Toxicity Category**
870.1100	Acute Oral- Rats	46684003	LD_{50} = 134/138 mg/kg	II
870.1200	Acute Dermal- Rabbits	47097627	LD_{50} > 5000 mg/kg	IV
870.1300	Acute Inhalation- Rats	47097628	LC_{50} = 1.96 mg/L	III
870.2400	Primary Eye Irritation- Rabbits	47097629	Minimally irritation	III
870.2500	Primary Skin Irritation- Rabbits	47097627	Not irritating	IV
870.2600	Dermal Sensitization- Guinea pigs	47097630	(positive)[1] (unacceptable study)	N/A

[1] In lieu of an acceptable dermal sensitization study demonstrating otherwise, TRB/RD recommends this chemical be labeled as a dermal sensitizer.

3.3 FQPA Considerations

3.3.1 Evidence of Neurotoxicity

There is no clear evidence of consistent neurotoxicity findings in the available toxicity studies. Findings of excessive salivation in the rat reproduction toxicity study are unlikely to be a sign of neurotoxicity since the chemical is not known to have a neurotoxic mode of action and no similar clinical findings were reported in the 90-day or chronic/carcinogenicity studies. It should be noted, however, that both later studies utilized a different strain (Fischer 344) than the one used in the reproduction study (Crl:CD (SD)BR, possibly a Sprague-Dawley strain). Another difference is that animals in the 90-day and chronic/carcinogenicity studies were administered fenazaquin by dietary feeding while gavage administration was used in the reproduction study.

According to the HED DER evaluation of the reproduction study, the finding of excessive salivation was dose-dependent and was well characterized showing a clear NOAEL/LOAEL (see executive summary under 3.2.3). During premating, the incidence of excessive salivation in the high-dose groups was 20/30 F_0 males, 14/30 F_0 females, 21/40 F_1 males, and 16/40 F_1 females (all $p \leq 0.01$). This finding was not seen in control animals and it occurred at low incidence in the low- and mid-dose groups (0-7 animals/group). The incidence of excessive salivation was also significantly increased in high-dose females of both generations during gestation and in high-dose F_0 females during lactation. Increased salivation was also reported in the high dose group of the preliminary one-generation reproduction study in addition to findings of impaired righting reflex (males: 1/10, females: 2/10) and decreased motor activity (females: 2/10) in the high dose group of the preliminary reproduction study.

The available remaining repeated dosing studies in rats, dogs or hamsters had no indications of treatment-related neurotoxicity including clinical signs, qualitative or quantitative neurobehavioral effects, brain weight changes, or gross/microscopic pathology findings.

Among the clinical findings in the available acute oral toxicity study were hypoactivity, ataxia, and hunched posture among surviving as well as moribund rats. In all likelihood, these clinical signs were due to the high acute toxicity of fenazaquin rather than being symptoms of neurotoxicity.

Therefore, based on the currently available data, HED, at this time, believes that conducting acute and subchronic neurotoxicity studies may not result in a NOAEL less than that of 5 mg/kg/day already set for fenazaquin and an additional uncertainty factor (UF_{DB}) for database uncertainties does not need to be applied.

3.3.2 Developmental Toxicity Studies

In both the rat and rabbit developmental toxicity studies, there is no evidence of increased quantitative or qualitative susceptibility following in utero exposure to fenazaquin. The rabbit developmental toxicity study is considered unacceptable/guideline due to lack of any maternal or developmental findings up to 60 mg/kg/day. This residual uncertainty should not impact the current evaluation because acute and chronic dietary endpoints are based on NOAEL/LOAEL of 10/40 and 5/25 mg/kg/day, respectively, which are well-below the high dose of 60 mg/kg/day in the rabbit developmental study. In addition, the rat is more sensitive to fenazaquin than the rabbit and a new developmental toxicity study in rabbits is not expected to affect the acute dietary end-point selection. Therefore, a new rabbit developmental study is not needed.

3.3.3 Reproductive Toxicity Study

There are no qualitative or quantitative pre-natal susceptibility issues and no residual uncertainties in the rat two-generation reproduction study.

3.3.4 Additional Information from Literature Sources

A recently published in vitro study suggests a possible role for fenazaquin in binding to and inhibition of mitochondrial complex I resulting in reduction of ATP and toxicity in neuroblastoma cells. (Sherer, T.B. et.al., J.Neurochemistry, March 2007; 100(6):1469-79).

3.3.5 Pre-and/or Postnatal Toxicity

3.3.5.1 Determination of Susceptibility

There are no qualitative or quantitative pre- or post-natal susceptibility issues based on available data from two developmental toxicity studies and a two-generation reproduction toxicity study.

3.3.5.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

As discussed above, there is no evidence of increased quantitative or qualitative susceptibility following in utero exposure to rats or rabbits. There are no residual uncertainties in the rat

developmental study because a clear NOAEL/LOAEL was established. In the rabbit developmental toxicity study, there were no maternal or developmental findings up to 60 mg/kg/day. As discussed above (3.3.3), this residual uncertainty should not impact the current evaluation because acute and chronic dietary endpoints are based on NOAEL/LOAEL of 10/40 and 5/25 mg/kg/day, respectively, which are well-below the high dose of 60 mg/kg/day in the rabbit developmental study. Also, there is no pre-/post-natal quantitative or qualitative susceptibility in the two-generation reproduction study and there are no residual uncertainties.

3.3.6 Recommendation for a Developmental Neurotoxicity Study

Not recommended at this time.

3.4 Classification of Carcinogenic Potential

At the request of the Registration Action Branch 3, in an *ad hoc* meeting, senior members of HED's Cancer Assessment Review Committee reviewed the carcinogenicity study in hamsters, as well as the carcinogenicity study conducted in rats, the mutagenicity studies, and discussed the possible carcinogenic mode of action of fenazaquin. Based on the weight of evidence of these studies, and in accordance with the 2005 Guidelines for Carcinogen Risk Assessment, the members concluded that the negative hamster findings along with the negative tumor findings in the 24-month rat study and negative mutagenicity findings support a cancer classification of "**Not likely to Be Carcinogenic to Humans**" for fenazaquin. In this meeting it was concluded that the carcinogenicity study in hamsters is "Acceptable/Guideline" and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in hamsters. Despite the enteritis and administration of antibiotics, the study is considered acceptable based on the adequacy of dosing based on evidence of systemic toxicity, acceptable survival rate at 17 months, and lack of evidence for tumorigenicity in two species, hamsters and rats.

3.5 Dermal Absorption Factor

There are no appropriate studies for estimating a dermal absorption. Therefore a default dermal absorption factor of 100% is used for estimating dermal exposure and risks.

3.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the

wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fenazaquin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health Data

There are no existing registered uses of fenazaquin in the U.S. Incident reports have not been identified.

5.0 Dietary Exposure/Risk Characterization

As listed in 40 CFR 180.632, permanent import tolerances have been established for residues of fenazaquin per se in/on the following raw agricultural commodities:

Apple	0.2 ppm
Pear	0.2 ppm
Fruit, citrus Group 10, except grapefruit	0.5 ppm
Citrus, oil	10.0 ppm

For this current assessment, contribution to dietary exposure from the above imported foods must be combined with the dietary contribution of fenazaquin residues in drinking water resulting from the proposed new non-food uses on Christmas tree plantations and ornamentals.

5.1 Pesticide Metabolism and Environmental Degradation

For a detailed discussion of the residue chemistry and tolerance assessment for the above food uses refer to:

HED: *"Fenazaquin. Request for Tolerances on Imported Apples, Pears and Citrus Fruits. Summary of Analytical Chemistry and Residue Data."* Danette Drew/David Soderberg, Reregistration Branch 3; Petition Number 9E5059; DP #: 329427, 04/26/07.

5.1.1 Metabolism in Rotational Crops

Rotational crop studies are not required as no food uses are currently being supported in the U.S. and the uses supported overseas are for perennial crops.

5.1.2 Analytical Methodology

A series of related gas chromatography/mass spectrometry detection (GC/MSD) methods are available for collecting data on fenazaquin residues in apples, pears, citrus fruits and their various processed fractions, and an HPLC/UV method is available for collecting data on fenazaquin

residues in apple juice. These methods were adequately validated in conjunction with the various field trials and processing studies. For each method, the validated limit of quantitation (LOQ) for fenazaquin is 0.01 ppm in all matrices, and the reported limit of detection (LOD) is 0.002 ppm. Independent laboratory validation (ILV) trials were conducted on the methods for determining residues in apple and orange commodities (whole fruit and juice). However, additional information must also be submitted for each of these ILV studies before the methods will be subjected to an Agency TMV (tolerance method validation). Adequate radiovalidation data, demonstrating the extraction efficiency of the proposed enforcement methods, were not submitted.

Although the proposed GC/MSD and HPLC/UV methods can not yet be approved for enforcing tolerances, the available data indicate that fenazaquin tolerances may be enforced using the existing FDA Multiresidue Methods in PAM, Vol I. Testing of fenazaquin through the multiresidue methods indicated that fenazaquin was adequately recovered from whole oranges using methods in Sections 302 and 303 and from orange oil using methods in Section 304. These data will be forwarded to the U.S. FDA. Radiovalidation data of the single analyte methods should be submitted for future petitions for tolerances on additional crops.

5.1.3 Pesticide Metabolites and Degradates of Concern

Ref: *"Fenazaquin. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS)."* George F. Kramer, DP #: 352321, 07/11/08.

Table 6. Summary of Metabolites and Environmental Transformation Products to be Included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop[1]	Parent	Parent
	Rotational Crop	N/A[1]	N/A[1]
Drinking Water		Parent	Not Applicable

1. Import tolerance only, and use on orchard fruits only.

Fenazaquin = 4-[[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline

Plants

The predominant residues in apples are fenazaquin and its dimer. [An unknown in the residues on the surface of apples was identified as a dimer of the parent that can also be artificially induced using UV-irradiation. Although this dimer was not specifically identified on oranges, its presence also has not been excluded.] Other metabolites did not exceed 10% of the total radioactive residue on these fruits. The dimer can be excluded as a residue of concern since it is unlikely to be cleaved back to the parent and it is not likely to be absorbed after ingestion due to

its high molecular weight. Therefore, no metabolites need to be included as residues of concern for these matrices.

Water

In drinking water, parent fenazaquin, 2-hydroxyfenazaquin (Metabolite 1, and its tautomeric keto form), 4-hydroxyquinazoline, and 4-t-butylphenylethanol are the predominant degradates. Because of their closeness in structure, it seems likely that 2-hydroxyfenazaquin and fenazaquin may share the same toxicity. However, 2-hydroxyfenazaquin can be excluded based upon exposure considerations as it was found at <10% of the residue. The two metabolites, 4-hydroxyquinazoline and 4-t-butylphenylethanol, are cleavage products that are expected to be readily excreted based on the rat metabolic pathway and no indication of bioaccumulation; the corresponding hazard would likely be low based on the parent compound toxicity profile (e.g., body weight changes and food efficiency decrease). SAR analysis (DEREK) did not reveal any structural alerts for these compounds. Based on these rationales, the two cleavage products can be excluded as residues of concern based on low-hazard considerations. Therefore, no degradates need to be included as residues of concern for drinking water.

For purposes of this registration action, finite residues of fenazaquin are not expected in livestock commodities. Tolerances for fenazaquin in livestock commodities may be required if future uses result in significant residues on livestock feedstuffs.

5.1.4 International Residue Limits

There are no established or proposed Canadian, Mexican or Codex MRLs for residues of fenazaquin in plant commodities (Appendix I). However, MRLs have been established for fenazaquin in/on citrus fruits in a number of countries at the following levels: 0.01 mg/kg in Belgium, Germany, and Luxembourg; 0.05 mg/kg in the United Kingdom; 0.2 mg/kg in Italy, Spain and Switzerland; 0.5 mg/kg in Portugal and Taiwan; and 0.7 mg/kg in Korea. There are also currently MRLs for fenazaquin in/on apples at 0.1 mg/kg in Germany and in/on pome fruits at 0.5 mg/kg in Taiwan.

5.2 Dietary (Food plus Drinking Water) Exposure and Risk

Ref: *"Fenazaquin Acute and Chronic Aggregate Dietary Exposure Assessment for the Section 3 Registration Action for Non-food use outdoors"* T. Moore. DP#344660. 08/27/08.

Acute and chronic dietary risk analyses were conducted with the DEEM-FCID™ model to form a conservative evaluation of exposure for fenazaquin. The acute dietary analysis made at the 95th percentile indicate risk estimates are reasonably below the 100% of the aPAD threshold level of concern for each population subgroup. For the most highly exposed population subgroup, children 1-2 years of age, acute dietary risk was estimated to be 24% of the aPAD with an exposure of 0.023546 mg/kg/day. In addition, chronic analysis yielded risk estimates well below the 100% of the cPAD threshold level of concern for each population subgroup. Likewise, for children 1-2 years of age, chronic dietary risk proved to be 13% of the cPAD with an exposure of

0.006251 mg/kg/day. An overview summarizing the results of the acute and chronic dietary assessments with the population subgroup having the highest exposure being noted in bold is presented in Table 7.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.007213	7	0.001474	3
All Infants (< 1 year old)	0.010328	10	0.002242	5
Children 1-2 years old	**0.023546**	**24**	**0.006251**	**13**
Children 3-5 years old	0.016832	17	0.004501	9
Children 6-12 years old	0.010225	10	0.002396	5
Youth 13-19 years old	0.017610	8	0.001416	3
Adults 20-49 years old	0.005044	5	0.000929	2
Adults 50+ years old	0.003926	4	0.000894	2
Females 13-49 years old	0.005567	6	0.001028	2

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The DEEM-FCID™ acute and chronic analyses assume that fenazaquin residues are in/on all registered food commodities at tolerance levels and that 100% of all the raw agricultural commodities (RACs) consumed domestically are treated imports.

5.4 Drinking Water Data

Ref: *"The Drinking Water Concentration for Fenazaquin 4-tert-butylphenethyl quinazolin-4-yl ether (IUPAC) 4-[[4-(1,1-dimethylethyl)phenyl]quinazoline*" S. C. Termes. DP# 350272. 07/29/08.

The drinking water residues provided by the Environmental Fate and Effects Division (EFED) were incorporated directly into the dietary assessment presented in Section 5.2 above. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct all sources" and "water, indirect, all sources."

The Environmental Fate and Effects Division (EFED) has performed Tier I estimates using the generic, FIRST model (FQPA Index Reservoir Screening Tool model). These concentrations are tabulated in Table 8. Should a refinement be needed in the future for new uses, the Division will provide Tier II estimates using PRZM and EXAMS.

Table 8. Tier I Estimated Concentrations of Fenazaquin in Untreated Drinking Water

Peak Day (acute) Concentration, μgL^{-1}	Annual Average (chronic) concentration, μgL^{-1}
2.632	0.064

The input parameters used in the FIRST simulation model were obtained from the environmental fate and physical-chemical properties submitted by petitioner in support of registration of fenazaquin. The use input parameters were extracted from the proposed label dated March 2008.

Modeled Uses (as per March 2008 Label):
Outdoor use: Non-food crops (foliage crops, Christmas tree plantations, ornamental plants, non-bearing tree fruits and nuts and established ornamental landscape plantings.

Model Description: http://www.epa.gov/oppefed1/models/water/index.htm#first

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

An emulsifiable concentrate liquid (GWN-1708) is intended for use by professional applicators to ornamental landscape plantings, including residential areas. While residues of fenazaquin may be present on the foliage after application, contact with the ornamentals by homeowners and their children is expected to be minimal. Therefore, residential exposure is expected to be negligible for this use and a residential exposure/risk assessment was not conducted.

7.0 Aggregate Risk Assessments and Risk Characterization

Because residential exposure to fenazaquin from its proposed use on ornamentals in residential areas is expected to be negligible, short-, intermediate-, and long-term aggregate assessments risk assessments are not required. However, the new uses result in drinking water exposures that must be aggregated with the dietary sources of fenazaquin resulting from tolerances on apples, pears and citrus fruits exported to the U.S. The aggregate exposure/risk assessment for the proposed new uses is limited to dietary only (food plus drinking water). See section 5.2 for estimates of the acute and chronic dietary (food plus drinking water) risks.

8.0 Cumulative Risk Characterization/Assessment

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 fenazaquin and any other substances. For the purposes of this action, therefore, EPA has not assumed that fenazaquin 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/.

9.0 Occupational Exposure/Risk Assessment

Short-term occupational handler exposure is possible via the dermal and inhalation routes, and short-/intermediate-term postapplication exposure may occur via the dermal route based on the proposed use pattern. Short-term dermal and inhalation endpoints were selected from a developmental toxicity study in the rat. Dermal and inhalation exposures were combined and then compared to the maternal NOAEL of 10 mg/kg/day. The endpoint includes decreased body weight gain, food intake, and food efficiency (Maternal LOAEL of 40 mg/kg/day). The intermediate-term dermal endpoint was selected from a 90-day feeding study in dogs. The dermal exposures were compared to the NOAEL of 5 mg/kg/day based on decreased body weight, body weight gains, food consumption and efficiency at the LOAEL of 15 mg/kg/day. No data are available regarding dermal absorption, therefore the default absorption rate of 100% was assumed. Toxicity by the inhalation route is assumed to be equivalent to oral toxicity. The level of concern (LOC) is a margin of exposure (MOE) less than 100 [10X for interspecies extrapolation and 10X for intraspecies variation].

9.1 Handler Exposure and Risk

There is a potential for exposure to fenazaquin during mixing, loading, and application activities. No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Standard Operating Procedure #7, dated 1/28/99).

Exposure inputs and risk estimates are summarized in Table 9. MOEs were first calculated for handlers wearing "baseline" clothing, which includes: long sleeve shirt, long pants, shoes and socks. For the scenarios that do not reach the LOC at baseline, results from adding personal protective equipment (PPE) are also presented. Most of the scenarios have MOEs above the LOC of 100 when gloves are added to baseline clothing but, the addition of coveralls is necessary for mixing/loading/applying with a high-pressure handwand. A dermal absorption or dermal toxicity study would be helpful in refining this scenario; the MOE of 89 is based on the conservative assumption of 100% dermal absorption.

When appropriate mitigation is used, none of the scenarios are of concern. Per the Worker Protection Standard (WPS), the minimum level of PPE for handlers is based on the acute toxicity of the end-use product. The Registration Division is responsible for ensuring that PPE listed on the product label is in compliance with WPS.

HED recognizes that it is feasible for the same individual to mix/load and apply formulations with the groundboom and airblast sprayers, however, appropriate data are not available in PHED for which unit exposure values for these combined activities can be derived. HED does not recommend simply adding the unit exposure values for each job function because any extrapolation error (i.e., exposure from the amount ai handled in the study to that of a real-life application) would be magnified, leading to greater uncertainty. Even with the over-estimation

uncertainty, the MOEs for these combined activities for groundboom and airblast application of fenazaquin would be above the LOC of 100 (i.e., ranging from 300 to 1,500).

Table 9. Summary of MOEs for Occupational Handlers of Fenazaquin

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai) [1]		Inhalation Unit Exposure (mg/lb ai)[2]	Use Site	Application Rate (lb ai/A)[3]	Area Treated (A/day)[4]	Daily Dose (mg/kg/day)[5]		Total Short-term MOE [6]	
	Baseline	PPE (gloves)					Dermal	Inhalation	Baseline	PPE (gloves)
Mixer/Loader										
Mixing/Loading Liquid for Groundboom application	2.9	0.023	0.0012	Ornamentals	0.30	40	0.50 0.0039 (gloves)	0.00021	20	2,400
Mixing/Loading Liquid for Airblast application	2.9	0.023	0.0012	Ornamentals	0.30	20	0.25 0.0020 (gloves)	0.00010	40	4,800
Applicator										
Applying Sprays with Open Cab Groundboom	0.014	-	0.00074	Ornamentals	0.30	40	0.0024	0.0013	4,000	-
Applying Sprays with Open Cab Airblast Sprayer	0.36	-	0.0045	Ornamentals	0.30	20	0.031	0.00039	320	-
Mixer/Loader/Applicator										
Mixing/Loading Liquid and Applying with High-Pressure Handwand	no data	2.5 1.58 (+ coveralls)	0.12	Ornamentals	0.0030 (lb ai/gal)	1,000 (gal/day)	0.11 (gloves) 0.068 (+ coveralls)	0.0051	no data	89 (gloves) 140 (+ coveralls)
Mixing/Loading Liquid and Applying with Backpack Sprayer	no data	2.5	0.03	Ornamentals	0.0030 (lb ai/gal)	40 (gal/day)	0.0043 (gloves)	0.000051	no data	2,300

[1] Baseline dermal unit exposure values represent long pants, long sleeved shirts, shoes, and socks; PPE values represent the addition of chemical-resistant gloves (and coveralls for the high-pressure handwand scenario) for those scenarios in which the MOEs do not reach 100 at baseline or those for which data are not available without gloves. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.

[2] Inhalation unit exposure values represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.

[3] Application rates are based on maximum values found in proposed label: GWN-1708 (Reg No. 10163-EOT).

[4] Daily area treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (standard EPA/OPP/HED values).

[5] Daily Dose (mg/kg/day) = Unit Exposure * % Absorption * Application rate * Area treated} / 70 kg; where dermal and inhalation absorption are assumed to be 100%.

[6] Short-Term MOE = NOAEL (10 mg/kg/day) / (Daily Dermal Dose + Daily Inhalation Dose). The LOC is an MOE of less than 100.

9.2 Occupational Postapplication Exposure and Risk

Occupational postapplication exposure is possible for workers entering treated areas to tend ornamentals in nurseries, greenhouses, and landscapes. Short- /intermediate-term postapplication exposure may occur via the dermal route based on the proposed use pattern.

Chemical-specific residue data were not submitted for fenazaquin, therefore, the standard assumption regarding dislodgeablity was used to estimate postapplication exposure (i.e., 20 percent of the application rate was used as the initial dislodgeable foliar residue). The transfer coefficients used in this assessment are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (policy # 3.1). It is the intention of HED's Science Advisory Council for Exposure that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

A summary of the occupational postapplication dermal exposure and risk assessment is provided in Table 10. The activities evaluated include hand pruning, harvesting, and burlapping containerized ornamentals. The short- and intermediate-term dermal MOEs for occupational postapplication are greater than the LOC of 100 on the day of application (indicating an REI of 12 hours); and therefore, are not of concern. The technical material has been classified in Toxicity Category IV for acute dermal and primary skin irritation, and Category III for primary eye irritation. Per the Worker Protection Standard (WPS), a 12-hr REI is required for chemicals classified under Toxicity Category III/IV. The proposed fenazaquin label (GWN-1708) specifies an REI of 12 hrs, which is in compliance with the WPS.

Table 10. Exposure and Risk Assessment for Occupational Postapplication Activities on Ornamentals

Days After Application (t)	Dislodgeable Foliar Residue ($\mu g/cm^2$)[1]	Transfer Coefficient (cm^2/hr)[2]	Activity[2]	Daily Dose[3] (mg/kg/day)	Dermal MOE[4]	
					Short-Term	Int-Term
0	0.67	100	Hand pruning	0.0077	1,300	650
0	0.67	400	Harvesting, ball/burlap	0.031	330	160

[1] Dislodgeable Foliar Residue, or DFR, ($\mu g/cm^2$) = Application rate (0.3 lb ai/A) x CF (4.54E+8 μg/lb) x CF (2.47E-8 A/cm^2) x Initial Fraction of ai Retained on the Foliage (standard value = 0.2)].

[2] Transfer coefficients are taken from the HED Science Advisory Council (SAC) for Exposure Policy 003.1 (August 2000), which include data supplied by the Agricultural Reentry Task Force.

[3] Daily Dose = (DFR x 100% dermal absorption x 0.001 mg/μg x Dermal Transfer Coefficient x 8-hr) / 70-kg Body weight

[4] MOE = NOAEL/Daily Dose; where Short-Term Dermal NOAEL = 10 mg/kg/day, and Intermediate-Term Dermal NOAEL = 5 mg/kg/day. The LOC is an MOE less than 100.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

870.6200a Acute Neurotox. Screening Battery (rat)
870.6200b 90 Day Neurotox. Screening Battery (rat)
870.7800 Immunotoxicity Study.
870.3200 28-Day Dermal

10.2 Residue Chemistry

Taken from HED: "*Fenazaquin: PP# 9E5059. Tolerances on Apples, Pears and Citrus Fruits Exported to the US. HED Risk Assessment.*" Jack Arthur, (RAB3), Decision #: 302678, DP #: 325204, 05/15/07.

- Although a general summary of the use directions on apples, pears and citrus fruits was provided, additional information is required detailing the maximum allowed use rates and minimum PHIs allowed for apples, pears and citrus fruits in each country in which these uses are allowed. Representative labels (and translations) should be submitted for each crop from the major growing regions (Europe, South America, and Asia).

- Radiovalidation data demonstrating the extraction efficiency of the proposed single analyte enforcement methods were not submitted. However, the available data indicate fenazaquin tolerances may be enforced using the existing FDA Multiresidue Methods in PAM, Vol I. Testing of fenazaquin through the multiresidue methods indicated that fenazaquin was adequately recovered from whole oranges and from orange oil. Radiovalidation data for the single analyte methods should be submitted with future petitions.

- For future petitions, the following information is needed for each of the ILV studies: (i) a description of the number of trials required to obtain the reported recovery values; (ii) a description of any problems encountered and a written description of any changes or modifications that were made to the method during the ILV; (iii) discussion of any steps considered critical; (iv) time required for analysis of one set of samples; and (v) details of communications between the independent laboratory and the method developers or others familiar with the method.

- Additional storage stability data are required on apples to support the sample storage intervals from the tests conducted on pears and apples in Argentina during 1993/94 and on apples in Chile during 1995. Data should be submitted demonstrating the stability of fenazaquin in frozen apples for intervals up to 25 months.

- A reference standard for fenazaquin must be submitted to the National Pesticide Standards Repository.

10.3 Occupational

The GWN-1708 label is not acceptable as written. The units expressing application rate need to be specified in terms of fluid ounces rather than ounces, as this is a liquid-type formulation. In addition, coveralls need to be added to the personal protective equipment (PPE) section for handlers using high-pressure handwands (a dermal absorption or dermal toxicity study would be helpful in refining this scenario). Finally, as noted in Table 5, in lieu of an acceptable dermal sensitization study demonstrating otherwise, TRB/RD recommends that this chemical be labeled as a dermal sensitizer.

ATTACHMENTS

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 4-[2-[4-(1,1-dimethylethyl)phenyl] ethoxy]quinazoline	Common Name: Fenazaquin	X Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 1/31/07
Codex Status (Maximum Residue Limits)		**U. S. Tolerances**	
__No Codex proposal step 6 or above X No Codex proposal step 6 or above for the crops requested		Petition Number: 9E5059 DP Barcode: D329427 Other Identifier:	
Residue definition (step 8/CXL): N/A		Reviewer/Branch: D. Drew/ RAB3	
		Residue definition: parent only	
Crop (s)[1]	MRL (mg/kg)	Crop(s)	Recommended Tolerance (ppm)
		Apple	0.2
		Pear	0.2
		Fruit, citrus, group 10	0.5
Limits for Canada		**Limits for Mexico**	
X No Limits __No Limits for the crops requested		__No Limits X No Limits for the crops requested	
Residue definition: N/A		Residue definition: N/A	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions:			

APPENDICES

Appendix A: Toxicology Assessment

A1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for imported foods for fenazaquin are in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1.1. Toxicology Data Requirements for Food Use - Fenazaquin

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	no	yes
870.1300 Acute Inhalation Toxicity	no	yes
870.2400 Primary Eye Irritation	no	yes
870.2500 Primary Dermal Irritation	no	yes
870.2600 Dermal Sensitization	no	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (dog)	yes	yes
870.3200 28-Day Dermal	yes	no
870.3465 28-Day Inhalation	no	---
870.3700a Developmental Toxicity (rat)	yes	yes
870.3700b Developmental Toxicity (rabbit)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rat)	yes	---
870.4100b Chronic Toxicity (dog)	yes	yes
870.4200a Oncogenicity (rat)	yes	---
870.4200b Carcinogenicity (hamster)	yes	yes
870.4300 Chronic Toxicity/Carcinogenicity (rat)	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Microneucleus – mammalian	yes	yes
870.5550 Mutagenicity—Unscheduled DNA - mammalian	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	---
870.6100b 90-Day Neurotoxicity (hen)	no	---
870.6200a Acute Neurotox. Screening Battery (rat)	yes	no
870.6200b 90 Day Neurotox. Screening Battery (rat)	yes	no
870.6300 Developmental Neurotoxicity	no	---
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	---
870.7800 Immunotoxicity	yes	no

A.2 Toxicity Profiles

Toxicity Profiles

Acute Toxicity Data - Fenazaquin Technical			
Study/ Species	MRID	Results	Toxicity Category
870.1100 Acute Oral (Rat)	46684003	LD_{50} = 134/138 mg/kg	II
870.1200 Acute Dermal, Rabbits	47097627	LD_{50} > 5000 mg/kg	IV
870.1300 Acute Inhalation, Rats	47097628	LC_{50} = 1.96 mg/L	III
870.2400 Primary Eye Irritation, Rabbits	47097629	Minimally irritation	III
870.2500 Primary Skin Irritation, Rabbits	47097627	Not irritating	IV
870.2600 Dermal Sensitization, Guinea pig	47097630	(positive)[1] (unacceptable study)	
1: In lieu of an acceptable dermal sensitization study demonstrating otherwise, TRB/RD recommends this chemical be labelled as a dermal sensitizer.			

Subchronic, Chronic and Other Toxicity Profile - Fenazaquin Technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat) (Fischer 344 from Charles River Laboratories Inc., Wilmington, MA)	45029904 (1992) Acceptable/guideline 0, 15, 45, 150, or 450 ppm M: .0, 1.0, 3.0, 9.6, and 28.7 mg/kg/d F: 0.0, 1.2, 3.5, 11.5, and 33.0 mg/kg/d	NOAEL = 9.6 mg/kg/day LOAEL = 28.7 mg/kg/day based on decreased body weight, body weight gain, and food consumption.
870.3100	90-Day oral (gavage) toxicity (rat) (Fischer 344 from Charles River Laboratories Inc., Wilmington, MA)	45029905 (1992) Acceptable/guideline 0, 1, 3, 10, or 30 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on decreased body weight, body weight gain, and food consumption/efficiency.
870.3100	90-Day oral toxicity (hamster)	45029903 (1992) Acceptable/guideline Males: 0, 5, 25, 75, or 150 mg/kg/day Females: 0, 5, 25, 50, or 100 mg/kg/day	NOAEL = 25 mg/kg/day LOAEL = 75/50 mg/kg/day (M/F) based on decreased body weight and testicular atrophy.
870.3150	90-Day oral toxicity (dog)	45029901 (1992) Acceptable/guideline 0, 1, 5, or 15 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on decreased body weight, body weight gain, and food consumption/efficiency.
870.3700a	Prenatal developmental (rat) (Crl:CD® (SD) BR from Charles River Laboratories Inc., Portage, Michigan)	45029911 (1989) Acceptable/guideline 0, 3, 10, 40 mg/kg/d	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 40 mg/kg/day based on findings (as early as GD 6-9) of decreased body weight gain, food intake, and food efficiency. **Developmental** NOAEL = 40 mg/kg/day LOAEL = > 40 mg/kg/day.
870.3700b	Prenatal developmental (rabbit)	45029912 (1990) Unacceptable/guideline 0, 3, 13, 60 mg/kg/d	**Maternal** NOAEL = 60 mg/kg/day LOAEL = > 60mg/kg/day based on lack of findings. **Developmental** NOAEL = 60 mg/kg/day LOAEL = > 60 mg/kg/day based on lack of findings.
870.3800	Reproduction and fertility effects (rat) (Crl:CD® (SD) BR from Charles River Breeding Laboratories, Raleigh, NC)	46684001 (1991) Acceptable/guideline 0, 1, 5, or 25 mg/kg/d	**Parental/Systemic** NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on excessive salivation and decreased body weight/weight gain and food intake. **Reproductive** NOAEL = 25 mg/kg/day LOAEL = >25 mg/kg/day. **Offspring** NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased weight gain during lactation.

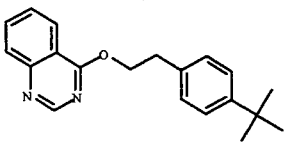
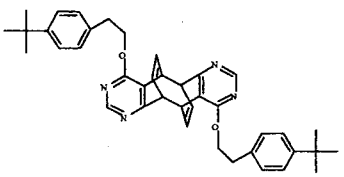
870.4300	Chronic toxicity/ Carcinogenicity Rat (Fischer 344 from Taconic Laboratory Animals and Services, Germantown, N.Y)	45029907 (1992) Acceptable/guideline 0, 10, 100, 200, or 400/450 (males/females) ppm M: .0.0, 0.46, 4.5, 9.2, and 18.3 mg/kg/d F: 0.0, 0.57, 5.7, 11.5, and 25.9 mg/kg/d	NOAEL = 9.2 mg/kg/day LOAEL = 18.3 mg/kg/day based on decreased body weight, body weight gain, and food consumption/efficiency.
870.4100	Chronic toxicity (dog)	45029906 (1993) Acceptable/guideline 0, 1, 5, or 12 mg/kg/d	NOAEL = 5 mg/kg/day LOAEL = 12 mg/kg/day based on decreased body weight, body weight gain, and food consumption/efficiency.
870.4200	Carcinogenicity (hamster)	45029913 (1992) Acceptable/guideline 0, 2, 15, or 30/35 (males/ females) mg/kg/d	NOAEL = 2/15 mg/kg/day (M/F) LOAEL = 15/35 mg/kg/day (M/F) based on decreased body weight (F) and body weight gain (M/F)-food consumption was not recorded. **No evidence of carcinogenicity**
870.5100	Gene Mutation Bacterial reverse mutation assay	44742909 (1989) Acceptable/guideline	**Negative** ± S9 up to 3000 µg/mL in the absence of cytotoxicity with precipitation above this concentration.
870.5300	Gene Mutation Mammalian cell culture (mouse lymphoma cells)	44742908 (1989) Acceptable/guideline	**Negative** –S9 severely cytotoxic at concentrations up to10 µg/mL **Positive** + S9 at concentrations (up to 12 µg/mL) that were severely cytotoxic (10-20% survival)
870.5375	Cytogenetics Chromosomal aberrations (CHO cells)	44742907 (1989) Acceptable/guideline	**Negative** ± S9 for clastogenic/aneugenic activity up to concentrations that reduced cell survival by ≈50% (1 µg/mL-S9; 60 µg/mL+S9). Compound precipitation was evident at levels ≥ 24 µg/mL +/- S9.
870.5395	Micronucleus Assay (mouse)	44742904 (1989) Acceptable/guideline	**Negative** for clastogenic/aneugenic activity in mouse bone marrow up to the highest dose tested in males/females (1600/1200 mg/kg, repeated on two days). In a preliminary study, the median lethal doses (MLD) were 3191/ 2430 mg/kg (M/F).
870.5915	*In vivo* SCE Assay (mouse)	44742905 (1989) Unacceptable/guideline (each data point had 3 males which is lower than the guideline recommended 5/sex/dose)	**Negative** in this cytogenetic assay (no increase in SCE) of bone marrow from male CD-1 mice treated with doses up to levels that produced death (2000 mg/kg).
870.5550	*In vitro* UDS Assay	44742906 (1989) Acceptable/guideline	**Negative** up to cytotoxic concentrations (≥0.5 to 1.0 µg/mL).

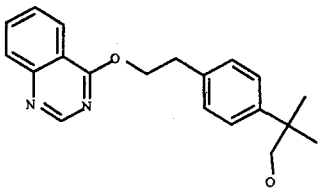
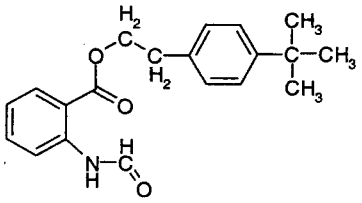
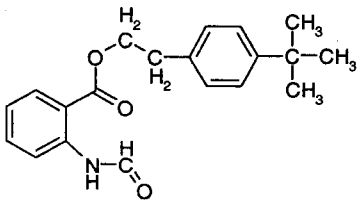
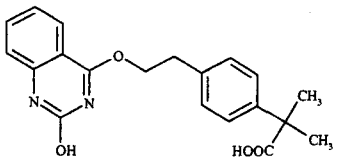
No Guideline	*In viro* UDS Assay	45029908 (1989) Acceptable/non-guideline	**Negative** for DNA damage and repair in this *in vivo/in vitro* test system up to the maximum tolerated dose (600 mg/kg).
870.7485	Metabolism and pharmacokinetics (species)	44742901 (1992) Unacceptable/guideline	Irrespective of dose, most of an orally administered radiolabeled fenazaquin was in rat excreta (89.5-107.7%) at 168 hours with approximately 20% of the radiolabel in urine. After initial uniform distribution, about 0.5-1.6% of the dose was in the carcass and below 0.04% of the dose in each tissue. There was no radiolabel in the expired air and no evidence for bioaccumulation. Based on excretion and tissue residue data, bioavailability is conservatively estimated at about 20% of an administered dose. Non-metabolized fenazaquin was higher in feces (1.0-15.0% of administered dose) than in urine (below 0.5% of dose) and some of the major metabolites were identified including AN-1 (urine) in addition to the fecal metabolites F-1, F-2 and F3. The metabolic pathway of fenazaquin involved cleavage of the ether bond, resulting in the formation of the respective alcohol (4-OH quinazoline metabolite) and carboxyl acid (AN-1) derivatives. Other biotransformation reactions included oxidation of one of the methyl groups on the alkyl side chain to produce either an alcohol (F-1) or carboxylic acid (F-2) metabolites. Finally, hydroxylation at the O-ether alkyl moiety of F-1 or the 2-position of the quinazoline ring of F-2 resulted in F-1A and F-3 metabolites, respectively.
Non-guideline	Special studies: Potential to induce hepatic hypertrophy and peroxisome acyl-CoA oxidase activity in mice	44742903 (1993) Acceptable/non-guideline	Fenazaquin and several of its analogs (with varying susceptibilities to metabolism of the ether bond or the alkylbenzene substituents) were assessed for their ability to increase liver peroxisomal fatty acyl-CoA oxidase (FAO, a marker of peroxisomal proliferation) and relative liver weight in groups of five CD-1 female mice. The FAO peroxisomal activity data indicate that oxidation of the t-butyl substituent on the alkylbenzene moiety (to the corresponding carboxylic acid) of fenazaquin and related compounds appears to be the critical step for heptatocellular peroxisome proliferation.

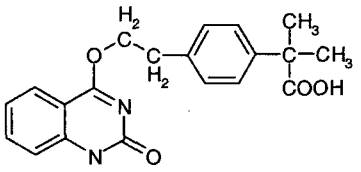
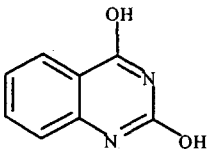
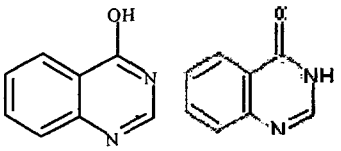
A.3 Executive Summaries

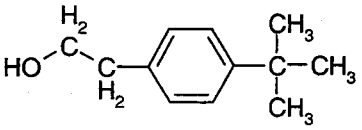
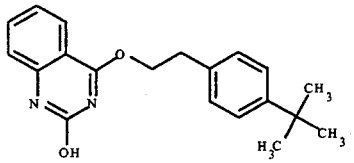
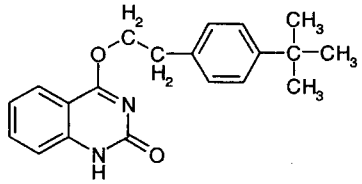
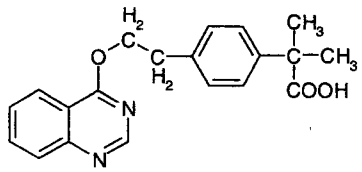
Refer to: HED: "*Fenazaquin: PP# 9E5059. Tolerances on Apples, Pears and Citrus Fruits Exported to the US. HED Risk Assessment.*" Jack Arthur, (RAB3), Decision #: 302678, DP #: 325204, 05/15/07.

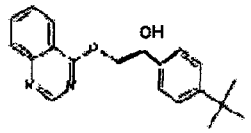
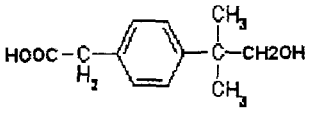
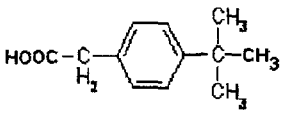
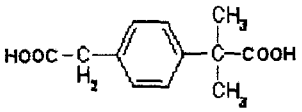
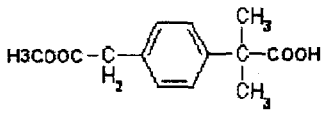
Appendix B. Tabular Summary of Metabolites and Environmental Transformation Products.

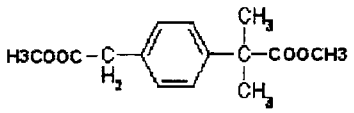
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
4-[[4-(1,1-dimethylethyl) phenyl]ethoxy]quinazoline (Fenazaquin) 	Apple - early season applic.	0-day PHI: 99.5 (1.154) [P] 99.6 (1.022) [Q]	
		28-day PHI: 48.0 (0.070) [P] 39.7 (0.085) [Q]	
		105-day PHI: 19.7 (0.009) [P] 14.8 (0.006) [Q]	
	Apple - late season applic	0-day PHI: 97.5 (0.903) [P] 97.8 (0.806) [Q]	
		70-day PHI: 23.6 (0.028) [P] 32.3 (0.054) [Q]	
	Orange - early season applic	191-day PHI: 52.0 (0.188) [P] 38.9 (0.126) [Q]	
	Orange - late season applic	63-day PHI: 65.5 (0.295) [P] 55.4 (0.500) [Q]	
	Ruminant (goat)	Tissues Fat: no quantitative data [P/Q]; however fenazaquin was the majority of the residue upon TLC separation	Tissues liver (trace): 0.1 (<0.001) [P] <0.1 (<0.001) [Q]
		Milk Sample only characterized,	Milk parent not identified
	Rat		1 – 21% of residue in feces
	Water	Major residue	
Fenazaquin Dimer 	Apple - early season applic	28-day PHI: 27.4 (0.040) [P] 19.4 (0.041) [Q]	
		105-day PHI: 21.8 (0.010) [P] 15.5 (0.006) [Q]	
	Apple - late season applic	70-day PHI: 33.2 (0.039) [P] 14.0 (0.023) [Q]	
	Orange		Nor found (but not looked for)
	Goat		Tissues - Not found
	Rat		Not found
	Water		Not found

Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
2-methyl-2-{4-[2-(quinazolin-4-yloxy)-ethyl]-phenyl}-propan-1-ol (Metabolite C, Metabolite F1) 	Apple - early season applic.		0-day PHI: 0.5 (0.005) [P]
			28-day PHI: 3.3 (0.005) [P] 0.4 (0.001) [Q]
			105-day PHI: 1.9 (0.001) [P]
	Orange		Not found
	Goat		Not found
	Rat		5-9.4% TRR
	Water		
Metabolite 3 2-(4-Tert-butylphenyl)ethyl 2-(formylamino)benzoate 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat		Not found
	Water		Identified as present but not quantified
Metabolite 4. 1-(4-Tert-butylphenyl)-2-(quinazolin-4-yloxy)ethanone 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat		Not found
	Water		Identified as present but not quantified
2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid Enol form of Metabolite D 	Apple -		105-day PHI: 0.8 (<0.001) [Q]
And tautomeric Keto form of Metabolite D or Metabolite 2 or Metabolite F3	Orange		Not found
	Goat		Not found

Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
2-Methyl-2-(4-{2-[(2-oxo-1,2-dihydroquinazolin-4-yl)oxy]ethyl}phenyl) propanoic acid 	Rat	6.5 – 12.6% of TRR in rat feces	
	Water		Minor product Identified as present in keto (amide) form but not quantified
Dihydroxyquinazaline 	Apple - early season applic		28-day PHI: 4.4 (0.009) [Q]
	Apple - late season applic		0-day PHI: 0.1 (0.001) [Q]
			70-day PHI: 0.3 (0.001) [Q]
	Orange		Not found
	Goat		Not found
	Rat		Not found
	Water		Identified – amount not reported
4-hydroxyquinazoline Enol tautomer Keto tautomer 4-Quinazolinol. Quinazolidinone 4-Hydroxyquinazoline CAS Reg. No. 491-36-1 (Metabolite J, metabolite 4-OH)  **Note that they are tautomers**	Apple - early season applic		28-day PHI: 3.2 (0.007) [Q]
			105-day PHI: 5.2 (0.002) [Q]
	Apple - late season applic		0-day PHI: 0.3 (0.003) [Q]
			70-day PHI: 4.1 (0.007) [Q]
	Orange		Not found
	Goat		Not found
	Rat		Minor component of feces reported in proposed metabolic scheme
	Water	Minor to major product in water depending upon conditions	
Metabolite L, Tertiarybutylphenylethanol 4-(1,1-Dimethylethyl)benzene-ethanol. 4-(*ter*-butylphenyl ethanol CAS Reg No. 5406-86-0	Apple	late season applic	0-day PHI: 0.6 (0.005) [P]
			0-day PHI: 1.2 (0.001) [P]
	Orange		Not found
	Goat		Not found
	Rat		Not found, but implied present by general oxidative metabolism and presence of metabolite AN-1

Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
	Water	Major to minor product depending upon conditions	
4-[2-(4-tert-butyl-phenyl)-ethoxy]-quinazolin-2-ol Enol form of Metabolite 1; 2-hydroxy-fenazaquin  And Tautomeric Keto form of Metabolite 1, AGR-291102 4-(2-(4-(1,1-imethylethyl)phenyl)ethoxy)quinazolone Identified as a maximum of 8.1% of the applied as is the single maximum identified/quantified product besides CO_2 	Apple	See enol form	
	Orange - early season applic		191-day PHI: 8.1 (0.029) [P] 4.9 (0.016) [Q]
	Orange - late season applic		63-day PHI: 0.9 (0.004) [P] 0.9 (0.008) [Q]
	Goat	Liver 4.0% TRR 0.009 ppm [P] 10.4, 0.038 ppm [Q] Kidney not analyzed	
	Rat		Not found, but implied by general oxidative metabolism, presence in goat tissues, and by the presence of metabolite F3 in the feces
	Water	8.1% of applied chemical	
Metabolite 5 or Metabolite F2 2-Methyl-2-(4-(2-((4-quinazolinyl)oxy)ethyl)phenyl)propionic acid. 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces	16-23% of TRR in rat feces	
	Water		Identified as present but not quantified

Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM)[1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
Metabolite F1A 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces		0.8-2.6% of TRR in rat feces
	Water		
Metabolite AN-1 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces		24 – 29% of TRR in rat urine
	Water		
Metabolite 6 (4-tertbutylphenyl)acetic acid 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces		Not found, but presence implied by general oxidative metabolism and presence of metabolite AN-1
	Water		Minor identified product
1-[3-(carboxymethyl)phenyl]-2-methylpropionic acid 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces		Not found
	Water		Minor identified product
2-[4-(-methoxy-2-oxoethylphenyl]-2-methylpropionic acid 	Apple		Not found
	Orange		Not found
	Goat		Not found
	Rat Feces		Not found
	Water		Minor identified product
Methyl-2-[4-(2—oxoethyl)phenyl]-	Apple		Not found

Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
2-methylpropanoate 	Orange		Not found
	Goat		Not found
	Rat Feces		Not found
	Water		Minor identified product
Apple; 45029914 & 45029917; 31 or 125 mg ai/L; unknown X rate; post-emergence (spray painted to fruit), early season or late season; 0, 7, 14, 28 and 105-day PHI (early season) or 0 and 70-day PHI (late season). Orange; 45054401 & 44742913; 0.4 lb ai/A; 1X rate; post-emergence (foliar), early season or late season; 0, 28, 112 and 191-day PHI (early season) or 0, 19, and 63-day PHI (late season). Goat; 44742912 & 45029916; 10.3 ppm; 74X TDB; 5 days; 16-hour PSI. Rat 1; MRID No.; dosing level; other specific			

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Chemical Name: Fenazaquin

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HED File Code: 14000 Risk Reviews
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File ID: DPD343610
Accession #: 000-00-0126

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