CAMAS TECHNOLOGIES

Camas Technologies, Inc. is an agricultural research, development and production company engaged in the identification and commercialization of novel bioactive compounds for plant health and crop protection with a primary emphasis on the floriculture and horticulture markets.

Rose: Powdery mildew infection 5 Days After Treatment with QWEL®

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Camas Technologies, Inc.
P.O. Box 1357
Broomfield, Colorado 80038

QWEL® Conquer Fungus Naturally

INTRODUCING

QWEL®

A LIQUID CONCENTRATE

Conquer Fungus Naturally

CAMAS TECHNOLOGIES

A New Natural Chemistry

QWEL® Fungicide

A new chemistry for reliable control of powdery mildew and leafspot

Roses: Heavy infection of powdery mildew before QWEL®® application.

QWEL® is a natural product fungicide, which provides outstanding control of powdery mildew and leaf spot in the greenhouse.

As a reduced risk product with a new mode of action which is substantially different from other greenhouse fungicides, QWEL® has shown no evidence of fungal resistance in greenhouse trials. It is ideally suited for use either alone, in combination with certain other chemistries, or in management rotation with other greenhouse fungicides.

University tested, this product has demonstrated its efficacy in both preventative and curative spray programs for greenhouse ornamentals. In trials, QWEL® has been shown to control and eradicate powdery mildew in the greenhouse in 3 to 5 days.

QWEL® combined with Pipron® fungicide can extend the greenhouse control of powdery mildew to 21 days or beyond.

Control of powdery mildew can be facilitated by good horticultural practices in conjunction with a comprehensive fungicide program including prevention and eradication.

Roses: Recovery from powdery mildew infection 3 days after treatment

QWEL® FUNGICIDE FEATURES

- Formulation from a naturally occurring plant substance
- EPA reduced risk classification
- No evidence of fungal resistance
- Rapidly absorbed by plant foliage
- Does not wash off when spray is dry
- New natural chemistry with new mode of action
- Effective as a fungal eradicant in 72 hours
- Compatible with Pipron® for longer term control
- Does not require additional surfactants or adjuvants

QWEL® BENEFITS

- Cost effective as both a preventative and an eradicant spray
- Application costs save on materials used per acre of plants
- Labor costs are reduced as a result of faster preparation and application, and longer times between spray intervals.
- Lack of fungal resistance increases cost-effectiveness in rotation programs

APPLICATION RATES

For powdery mildew control:

1. For light infections dilute 3 ounces of QWEL® in 10 gallons of water; for heavy infections use 5 ounces per 10 gallons.
2. Apply to 2000 sq ft of plants to wet all foliage.
3. For roses and large plants apply to 1250 – 1500 sq ft to wet all foliage.

Reapply foliar sprays at 8 to 10 day intervals as needed. Use higher rates under heavy disease pressure. Lower rates may be used for subsequent applications and for preventative sprays.

Control in Combination with Pipron® :

1. For best results mix 4 ounces of Pipron® and 50 ounces of QWEL® with 100 gallons of water.
2. Apply to 20,000 sq feet of plants to wet all foliage.
3. For large plants and roses apply to 12,500-15,000 sq feet to wet all foliage.

For preventative or eradication control continue treatment at 21 day intervals or shorter periods if disease pressure warrants.

For leafspot control:

For leafspot control in container grown greenhouse ornamentals, treat plants at the rate indicated for heavy powdery mildew control and at 8-10 day intervals thereafter.

*Pipron® is a registered trademark of SePRO Corporation.

Camas Technologies Inc.

QWEL® Liquid Concentrate

Ornamental Plant Fungicide for use in Enclosed Commercial Greenhouses

Active Ingredient: Macleaya extract..... 1.5% by wt
Inert Ingredients..... 98.5% by wt
Total 100.0%
(Contains 0.125 lb active ingredient per gallon)
This product contains methanol.

KEEP OUT OF REACH OF CHILDREN

DANGER

FIRST AID

Si Usted no entiende la etiqueta, busque a alguien para que se la explique a Usted in detalle. (If you do not understand the label, find someone to explain it to you in detail.)
Read entire label and use in accordance with precautionary statements, directions and applicable regulations.

If in eyes	**Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, continue rinsing eye. Call a poison control center or doctor for treatment advice.**
If on skin or clothing	**Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.**
If swallowed	**Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything by mouth to an unconscious person.**

NOTE: Have the product container or label with you when calling a poison control center or doctor, or when going for treatment.
NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

EPA REG. NO.: 69876-1
ESTABLISHMENT NO.: 69876-CO-001
NET CONTENTS: 1 gallon (128 fl. oz.)
US Patent No. 6277416

MANUFACTURED BY: Camas Technologies, Inc.
P.O. Box 1357
Broomfield, CO 80038-1357

DIRECTIONS FOR USE:

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

- Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application.
- For any requirements specific to your State or Tribe, consult the Agency responsible for pesticide registration.

AGRICULTURAL USE REQUIREMENTS

Use this product only in accordance with its labeling and with the Worker Protection Standard (WPS) 40 CFR Part 170. This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emregency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personnel protective equipment (PPE) and restricted-entry interval. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.

PPE required for early re-entry to treated areas that is permitted under the WPS and that involves contact with anything that has been treated such as plants is:

- coveralls over long-sleeved shirt and long pants
- protective eyewear
- chemical-resistant gloves made of any waterproof material
- shoes with socks

- Apply this product only as a spray mist to control the indicated powdery mildews and leafspots on ornamental plants in a commercial greenhouse.
- Do not apply product through any type of irrigation equipment.

HAZARD TO HUMANS AND DOMESTIC ANIMALS

DANGER: Corrosive. Causes irreversible eye damage. Harmful if swallowed or absorbed through the skin. Do not get in eyes or on clothing. Avoid contact with the skin. Methanol may cause blindness.

PERSONAL PROTECTIVE EQUIPMENT: Applicators and handlers must wear long-sleeved shirt and long pants, shoes and socks. Applicators and handlers must use protective eyewear and wear chemical-resistant gloves made of any waterproof material. Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this liquid concentrate. Wash contaminated clothing before reuse. Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Store and wash PPE separately from other laundry.

User Safety Recommendations: Users should wash hands before eating, drinking, using tobacco or chewing gum or using the toilet. Remove clothing immediately if soaked with pesticide, wash thoroughly and put on clean clothing. Remove PPE immediately after handling this product. Wash outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

PHYSICAL AND CHEMICAL HAZARDS: Combustible. Do not use or store near heat or open flame.

GENERAL USE INFORMATION: QWEL (CTI 13-19B)-LC ornamental fungicide is a liquid concentrate containing botanical extracts of *Macleaya spp.* and is recommended for the control of certain fungal diseases of nursery annual, perennial and herbaceous ornamental plants grown in greenhouses.Best results are achieved when diluted according to directions and applied to plants as a foliar spray at the first sign of the disease. If disease is severe or reappears, the plants should be re-treated. See use and rate recommendations for applications and intervals for retreating.

Best results are achieved when used in a treatment program following the recommended rates and application directions.

CAREFULLY READ, UNDERSTAND AND FOLLOW ALL LABEL DIRECTIONS.

FOR ORNAMENTAL PLANTS: QWEL (CTI 13-19B)-LC ornamental fungicide is recommended for the control of certain diseases of annual, perennial and herbaceous ornamental plants in commercial greenhouses when applied as a foliar spray.

DISEASES CONTROLLED	Fungi
Powdery Mildews	Sphaerotheca pannosa, Erysiphe spp., Oidium spp., Podosphaera spp., Microsphaera
Leafspot	Alternaria, Septoria

ORNAMENTAL PLANTS FOR WHICH QWEL (CTI 13-19B)-LC IS RECOMMENDED. The following plants may be affected by the diseases and pest species listed above.

Ageratum	Ajuga	Alyssum	Arborvitae	Aster
Carnation	Coleus	Columbine	Cyclamen	Daisy
Dahlia	Delphinium	Euonymus	Ficus	Geranium
Hollyhock	Hydrangia	Impatiens	Lilac	Lily
Pansy	Petunia	Philodendron	Phlox	Poinsettia
Rhododendron	Rose	Snapdragon	Statice	
Strawflower	Verbena	Willow	Zinnia	

PLANT TOLERANCE: Neither the manufacturer nor the seller has determined whether or not **QWEL (CTI 13-19B)-LC** can be used safely on all species of ornamental plants. Before any large scale application, user should determine the safety of **QWEL (CTI 13-19B)-LC**. We recommend a small preliminary application trial to determine plant tolerance. Observe treated plants for foliage burn, stunting, staining or discoloration.

MIXING INSTRUCTIONS: Fill the sprayer tank with the required amount of water and add the recommended quantity of **QWEL (CTI 13-19B)-LC**. Agitate to mix thoroughly. Apply as a foliar spray with backpack or high pressure sprayer.

GENERAL USE PRECAUTIONS:

- **FOR PREPARATION USE WATER OF pH <7.5 WITH CARBONATE CONTENT <200 PPM ($CaCO_3$ or <240 PPM H_2CO_3).**
- **DO NOT ADD ANY TYPE OF ADJUVANT, SURFACTANT OR BUFFER WHEN PREPARING QWEL (CTI 13-19B)-LC FOR APPLICATION.**
- **SOME ROSE CULTIVARS MAY BE SUBJECT TO SLIGHT STAINING OR DISCOLORATION OF THE BLOOMS OR STEMS.**

APPLICATION RATE RECOMMENDATIONS:

For light infections:	**Use 3 fl. oz. in 10 gallons of water and apply as foliar spray to 2000 sq. ft. to wet all foliage. For roses and large plants, apply 10 gallons to 1250-1500 sq. ft.**
For heavy infections:	**Use 4 to 5 fl. oz. in 10 gallons of water and apply as foliar spray to 2000 sq. ft. to wet all foliate. For roses and large plants, apply 10 gallons to 1250-1500 sq. ft.**
Reapplication:	**Apply foliar sprays at 8-10 day intervals as needed. Use higher rates under heavy disease pressure. Lower rates may be used for subsequent applications and for preventive sprays.**

STORAGE AND DISPOSAL: Do not contaminate water, food or feed by storage and disposal.

Pesticide Storage: Store in cool, dry place. Store in original container. Keep tightly closed. Do not reuse empty container.

Pesticide Disposal: Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of Federal Law. If these wastes cannot be disposed of by use according to label instructions, contact our State Pesticide or Environmental Control Agency, or Hazardous Waste representative at the nearest EPA regional office for guidance.

Container Disposal: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by incineration, or if allowed by state and local authorities, by burning. If burned, stay out of smoke.

IMPORTANT NOTICE:

Warranty: The directions and recommendations on this label are derived from research to ensure correct product usage. The Manufacturer and Seller warrant that this product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with the directions and instructions specified on the label, but neither this warranty nor any other warranty of merchantability or fitness for a particular purpose, expressed or implied, extends to use of this product contrary to label instructions or under conditions not reasonably foreseeable to seller, and buyer and user assume all risk for such use. Camas Technologies, Inc. is not responsible for losses or damage resulting from the use of **QWEL (CTI 13-19B)-LC** in any manner not specifically recommended on the label.

Inherent risks of use: It is impossible to eliminate all risks associated with use of this product. Plant injury, lack of performance, or other unintended consequences may result because of such factors as use of the product contrary to labe instructions (including conditions noted on the label such as use of high carbonate water, or the addition of adjuvants, surfactants or buffers when preparing **QWEL (CTI 13-19B)-LC** for application or the inadequate testing, or failure to test for plant tolerance, etc.), manner of application or other factors, all of which are beyond the control of the Manufacturer or Seller. All such risks shall be assumed by the Buyer.

QWEL® Greenhouse Fungicide Trial Summary

Camas Technologies, Inc. has developed a novel agricultural fungicide for greenhouse use. The product was based on the application of the active natural substances known as quaternary benzophenanthridine alkaloids (QBAs) for plant protection applications. The company has recently received United States patent protection for the application of QBAs to plants.

The company isolates the active natural substances which are plant extracts in a proprietary and highly cost effective manner. Stable formulations of the concentrated extract have been developed for the treatment of fungal pathogens on plants. These formulations which are effective in commercial practice for the control of greenhouse fungal diseases which cause significant negative financial impacts in the ornamental and food crop plant industry. Formulation patents are currently pending in a number of countries world-wide.

The product formulation and technical grade active ingredient (QBAs) is registered with the Environmental Protection Agency (EPA) as a control for several fungal pathogens in the greenhouse industry (ornamental plants). The product is classified as a reduced risk pesticide, and present label carries a 12 hour REI. Table I and 11 attached to this document list the in vitro antibacterial and in vitro anti-fungal activities of one of the components of Macleaya Extract (CAS # 112025-60-2) which is the active ingredient found in QWEL® at a concentration of 1.5% by weight.

A partial summary of field trials results is set forth below.

TRIAL/LOCATION	PLANT/FUNGAL PATHOGEN	RESULTS
Colorado State/S Newman	Rose/Powdery Mildew (Sphaerotheca)	Curative
Gulley Greenhouses/S. Newman	Various plants/Powdery Mildew	Curative
Gulley Greenhouses/S. Newman	Various plants/Rusts	Not Effective
Welby Gardens/S. Newman	Zinnias/Roses/ Mildews	Curative
Pikes Peak Greenhouses/T. Haley	Roses (Tango)/Mildew	Curative
Franktown Floral/S. Newman	Roses/Mildew	Curative
Michigan State/M. Hausbeck	Miniature Roses/Mildew	Curative
Michigan State/M. Hausbeck	Miniature Roses/Mildew w Pipron	Curative
Nebraska/E. Paparozzi	Miniature Roses/Mildew	Curative
Chase Gardens/A. Chase	Geraniums/Botrytis	Not Effective
Chase Gardens/A. Chase	Raphioleps/Entomosporium	Control
Chase Gardens/A. Chase	Impatiens/Alternaria	Curative
Kitiyama Bros/M. Roll	Roses/Mildew	Curative
Colorado State/R. Zink(97)	Potatoes/Early Blight	Increased Yield (18%)
Colorado State/R. Zink (98)	Potatoes/Early Blight	Increased Yield (23%)
Grape Downy Mildew/Green	Grapes/Downy Mildew	Control (96 hr)
Colorado State/H. Larsen	Apples/Powdery Mildew	No Control
Colorado State/ R. Davidson	Potato Seed Piece/Fusarium	Control 13% Yield Increase

The product has shown to have limited phytotoxicity when applied in accordance with label instructions. There is little leaf or petal staining when applied at the recommended dilutions. In tank mix with Pipron, the product has demonstrated short and long-term fungicidal and fungistatic activity. Limited field trials have been conducted on large-scale agriculture crops as the initial focus of the company has been on the greenhouse and ornamental markets.

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A Naturally Occurring Compound for Controlling Powdery Mildew of Greenhouse Roses

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Additional index words. biorational pesticides, *Rosa*, *Sphaerotheca pannosa*

Abstract. **Quaternary benzophenanthridine alkaloids (QBAs) isolated from plants in the family Papaveraceae are effective for the control of some fungal diseases. Extracts from *Macleaya cordata*, a species rich in QBAs, were formulated at 150 mg·L^{-1} QBA for spray application to greenhouse roses (*Rosa* sp.) infected with *Sphaerotheca pannosa* var. *rosae* (powdery mildew). The QBA formulation was applied at 10-day intervals. For comparison, copper sulfate pentahydrate, piperalin, and fenarimol also were applied to mildew-infected plants within the same greenhouse at their respective labeled rates. One day after treatment, visible symptoms of mildew infection were reduced 60% by QBA, whereas fenarimol, copper sulfate pentahydrate, and piperalin reduced the symptoms of infection 50%, 75%, and 85%, respectively. Subsequent studies demonstrated that a tank mix of QBA and piperalin provided enhanced control of powdery mildew on rose. Results from this study indicate that QBAs have the potential to be developed as a biorational fungicide for greenhouse use with both fungicidal and fungistatic activity.**

Quaternary benzophenanthridine alkaloids (QBAs) are effective in the control of some fungal diseases of garden and ornamental crops (Howell et al., 1973). The QBAs belong to a large group of isoquinoline alkaloids biosynthesized from phenylalanine (Harkrader et al., 1990). They are widely distributed in nature and can be found in plants of the families Papaveraceae, Fumariaceae, and Rutaceae. Biological activities and pharmacological properties of the benzophenanthridine alkaloids have been elucidated and their biological safety range, as well as their interactions with biological systems, have been determined. These activities include antimicrobial (Godowski, 1989), antifungal (Vichkanova and Adgina, 1971), anti-inflammatory (Lenfield et al., 1981), antiprotozoal (Vichkanova et al., 1969), and sodium/potassium ATPase effects (Pitts and Meyerson, 1981). They inhibit the activity of protein kinase C (Herbert et al., 1991), acetylcholinesterase (Ultrichova et al., 1983b), butyryl cholinesterase (Ultrichova et al., 1983a), alanine aminotransferase (Walternova et al., 1981), and collagenase and bone resorption (Sakamoto, 1986), as well as photophosphorylation (Vallejos, 1973) and respiration (Vallejos and Roveri, 1972). These compounds also act as nematicides (Onda et al., 1965), macrophage cell activators, and positive inotropic agents on cardiac muscle (Agarwal et al., 1991).

The major QBAs are sanguinarine and chelerythrine. The richest natural sources of these two alkaloids are the plants *Sanguinaria canadensis* L., *Dicranostigma lacucoides* Hook.f. & T. Thoms., and *Chelidonium majus* L., which are found throughout the world (Harkrader et al., 1991). *Sanguinaria canadensis* (sanguinaria) is a perennial herb occurring widely in the eastern parts of North America (Bailey and Bailey, 1976). Common names in American literature for this plant include red root, blood root, puccoon root, and tetterwort (Martin, 1984). Sanguinaria was one of the first species to be investigated for its alkaloid content because of its conspicuous appearance and folkloric accounts of its use as a natural medicine. *Macleaya cordata* (Willd.) R. Br. is a perennial plant native to temperate regions of China and Japan (Bailey and Bailey, 1976). The benzophenanthridine alkaloid content of *Macleaya cordata* is 0.5% to 2% (Harkrader et al., 1991).

Sanguinarine is fungistatic on several plant fungal pathogens, including *Phytomatotrichum omnivorum* (Duggar) Hennebert, *Sclerotium rolfisii* Sacc., *Gaeumannomyces graminis* (Sacc.) Arx and D. Oliver (*Ophiobolus graminis*), *Rhizoctonia solani* Kühn, *Amillaria mellea* (Vahl: Fr.) Kummer, *Fusarium oxysporum* Schlecht. (*F. vasinfectum*), and *Verticillium albo-atrum* Reinke and Berthier (Greathouse, 1939; Greathouse and Rigler, 1940; Howell et al., 1973; Presley, 1969). All of these aforementioned studies were conducted in vitro. No reports of the application of QBAs directly to plants for the control of fungal pathogens have been found in the literature.

Laboratory studies with rats fed a diet for 14 d with up to 150 mg·L^{-1} sanguinarine, a benzophenanthridine alkaloid, showed no toxic effects (Becci et al., 1987). Evaluations of reproductive and developmental toxicology showed that orally administered sanguinarine had no adverse effects on estrous cycling, male or female copulatory and fertility indices, or gestation/lactation parameters of rats fed 10–100 mg·kg^{-1} per day (Keller and Meyer, 1989). Human clinical studies using commercial dentifrice samples (0.2% sanguinarine formulation) repeatedly applied to oral mucosal tissues showed no treatment-related lesions (Frankos et al., 1990). The fungistatic sanguinarine concentrations ranged from 2.5 to 320 µg·mL^{-1} in these tests.

The objective of the study reported here was to compare a fungicide formulated with QBAs extracted from *Macleaya cordata* with commercial fungicides for control of powdery mildew infecting greenhouse roses.

Materials and Methods

Hybrid rose plants, cultivars Gabriella, Royalty, Samantha, and Sonia, were established in granulated rockwool (Par-gro medium grade rockwool), in a single layer, fiberglass-reinforced plastic greenhouse. Plants were placed one per 0.093 m^2 in groups of 30 per block with each of two 1.07 × 10.7-m benches containing all four cultivars. Groups of cultivars were randomized on each bench. Plants were irrigated daily with a liquid nutrient solution containing (mg·L^{-1}) 200 N, 13 P, 264 K, and 16 Mg. Micronutrients were supplied by a soluble trace element mix (STEM; The Scotts Co., Marysville, Ohio) at 0.96 S, 0.22 Cu, 0.51 Fe, 0.55 Mn, 0.0027 Mo, 0.31 Zn, and 0.093 B mg·L^{-1}. Iron was supplied by Sequestrene 330 at 0.20 mg·L^{-1}.

Greenhouse conditions conducive to powdery mildew development were maintained during Fall 1995 and Winter 1996 for preliminary studies. The temperature was maintained at 22 ± 2 °C day and 19 ± 2 °C night. At the end of each day, the gravel floors were sprayed with water to increase the humidity in the greenhouses, encouraging *Sphaerotheca pannosa* (Wallr.: Fr.) Lêv var. *rosae* Woronichin (powdery mildew) infection.

Expt. 1. After powdery mildew infection was established at a minimum of 20% of the total leaf area, three concentrations of a *Macleaya cordata* QBA fungicide formulation, 75, 150, or 300 mg·L^{-1} (Camas Technologies, Broomfield, Colo.) and a control (water) treatment were applied onto leaflet surfaces to the point of drip in the greenhouse. The control was a plain water spray, which is a treatment often used by rose growers as an effective mildew control strategy for slight infections. The four treatments were randomly applied to two blocks of each cultivar. The degree of mycelial development was rated 4, 7, and 11 d

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[3]President.

after application. Mildew infection was rated visually as a percentage of total coverage on morphologically similar, five-leaflet leaves tagged on four stems of each cultivar in each block. The percentage of reduction of mycelium coverage relative to the initial leaflet coverage was determined.

Expt. 2. After the first experiment was terminated, the mildew infection was allowed to proceed at a level equal to or greater than 35% of the total leaf area. The QBA fungicide formulation was applied at 150 mg·L^{-1} to one block of the rose plants as previously described. To the other four blocks of rose plants, copper sulfate pentahydrate (Phyton-27 5.5EC; Source Technology Biologicals, Minneapolis), piperalin (Pipron 82.4EC; SePro Corp., Carmel, Ind.), fenarimol (Rubigan 12.5EC; DowElanco, Indianapolis, Ind.), and a water control were applied to mildew-infected plants at their respective label rates. With piperalin, 1.3 mL·L^{-1} potassium salts of fatty acids (insecticidal soap, M-Pede; Mycogen Corp., San Diego) was added as a surfactant. All products were applied at 10-d intervals. Mildew infection was rated visually as previously described, and the percentage of mycelium coverage compared with the water control.

Expts. 3 and 4. The next two studies were conducted during Dec. 1996 and Jan. 1997 using the original rose plants. As previously described, the greenhouse environment was conducive to powdery mildew development, which was allowed to establish at a level equal to or >35% for each study. For each study, the QBA fungicide formulation was applied at 75 mg·L^{-1}, one-half the previous rate. This rate was selected after noting that the effect of this treatment was similar to that obtained at higher rates 10 d after application. Copper sulfate pentahydrate, piperalin, and fenarimol were applied to mildew-infected plants at their respective label rates for comparison as previously described; water sprays were again used as the control. An additional treatment was included, which was a "tank mix" of piperalin at its labeled rate, combined with QBA at 75 mg·L^{-1}. No surfactant was included in this tank mix because the surfactant levels in the QBA formulation were adequate for piperalin performance. During the December study, a second application was applied after 6 d and a third 18 d later. During the January study, the second application was applied after 7 d and the third 10 d later. Mildew infection was rated visually as previously described. Infection data were analyzed as the percentage of reduction of mycelium coverage based on the initial leaflet coverage.

Expt. 5. A final trial to demonstrate the efficacy of QBA control of powdery mildew on greenhouse roses was conducted during September 1997 at two commercial cut-rose greenhouses. Franktown Floral (Franktown, Colo.) and Pikes Peak Greenhouses (Colorado Springs, Colo.) were chosen as the evaluation sites; each greenhouse had a resident infection of powdery mildew. At Franktown Floral, four QBA treatments were applied to 'Royalty' roses; these were an untreated control, a plain water spray, and QBA formulation rates of 25 and 50 mg·L^{-1}. At Pikes Peak Greenhouse, six treatments were applied to 'Gabriella' roses, including two controls as previously described, and five QBA formulation rates (12.5, 25, 38, 50, and 75 mg·L^{-1}). Lower rates were evaluated to determine a minimum level of efficacy of the QBA. Mildew infection was rated visually as previously described, but using five stems. Infection data were analyzed as the percentage of reduction of mycelium coverage compared with the initial leaflet coverage 8 d after product application.

Results and Discussion

Under our greenhouse conditions, the hybrid rose cultivars Gabriella, Royalty, Samantha, and Sonia all were equally susceptible to powdery mildew infection. In each subsequent study, no differences due to cultivar were detected; therefore, data for all cultivars were pooled.

Expt. 1. In the 1995–96 study, all rates of the QBA fungicide formulation had significantly reduced mildew infection after 15 d (Fig. 1). The 150-mg·L^{-1} QBA was the rate selected for the next study.

Expt. 2. Three days after treatment, the effect of the QBA fungicide formulation was similar to that of commercial fungicides fenarimol, copper sulfate pentahydrate, and piperalin in controlling powdery mildew (Fig. 2). The same was true after 7 d (data not shown). Piperalin and copper sulfate pentahydrate are both fungal eradicants and eliminate mildews quickly, but have little residual activity, thus requiring applications every 5 to 10 d (Powell, 1998). Fenarimol, a demethylation-inhibiting fungicide (van den Brink et al., 1996), serves as a protectant/eradicant for control of powdery mildews, and has long-term residual activity (Powell, 1998). Piperalin is a potent inhibitor of growth and ergosterol biosynthesis in sporidia of *Ustilago maydis* (DC.) Cda. (Schneegurt and Henry, 1992). Rose growers often rotate piperalin with fenarimol for residual, as well as protectant, disease management (Powell, 1998).

The broad-spectrum antimicrobial activity of QBAs appears to involve the inhibition of specific enzymes. Sanguinarine and chelerythrine break down the inner electron-dense layer of the cell walls of *Pseudomonas aeruginosa* (Schroeter) Migula and deform partitions between daughter cells. At higher QBA levels, bacterial cell walls also become thinner, and cell aggregation occurs (Beekov et al., 1983). Many other enzyme activities may be competitively or noncompetitively inhibited by QBAs, depending on the enzyme in question (Godowski, 1989). Whether the antifungal activity demonstrated in this study reflects inhibition of a specific enzyme activity was not determined.

Expts. 3 and 4. Many growers routinely tank-mix piperalin with thiophanate-methyl

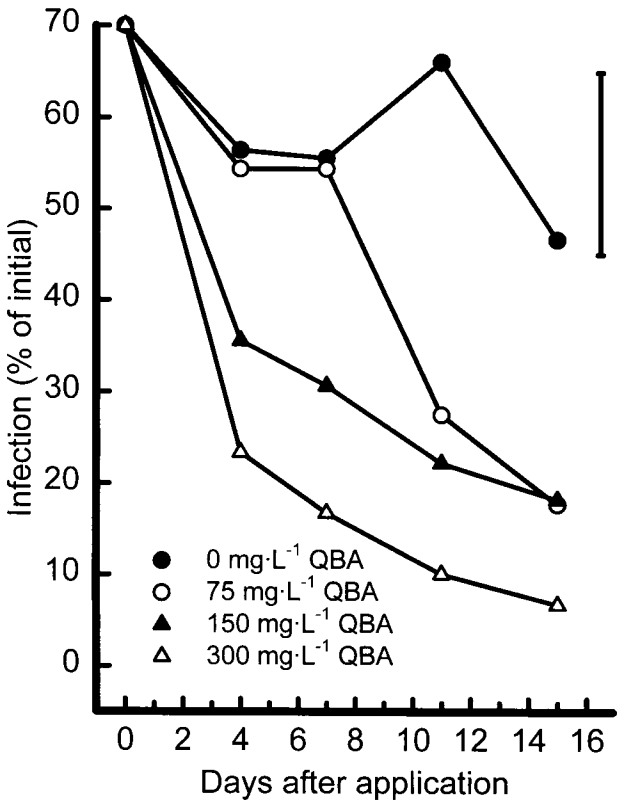

Fig. 1. Effect of concentration of quaternary benzophenanthridine alkaloids (QBAs) on percentage of reduction of *Sphaerotheca pannosa* var. *rosae* (powdery mildew) infecting greenhouse roses. Each mean represents 32 observations from the four cultivars ('Gabriella', 'Royalty', 'Samantha', and 'Sonia') pooled. Vertical bars represent least significant differences at $P \leq 0.05$.

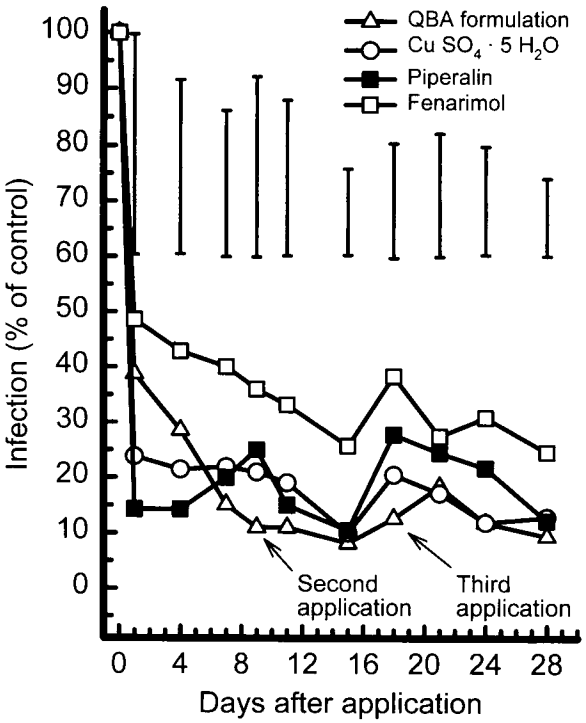

Fig. 2. Effect of quaternary benzylphananthridine alkaloids (QBAs), $CuSO_4 \cdot 5\ SO_4$, piperalin, fenarimol, and a water control applied at 10-d intervals on percentage of reduction of *Sphaerotheca pannosa* var. *rosae* (powdery mildew) infecting greenhouse roses. Each mean represents 32 observations from the four cultivars ('Gabriella', 'Royalty', 'Samantha', and 'Sonia') pooled. Vertical bars represent least significant differences at $P \leq 0.05$.

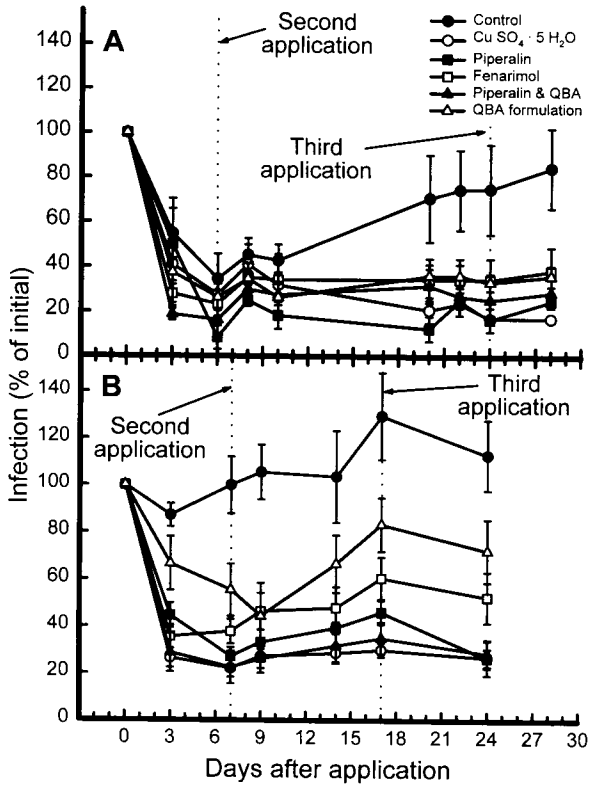

Fig. 3. Effects of application of quaternary benzylphananthridine alkaloids (QBAs), $CuSO_4 \cdot 5\ SO_4$, piperalin, fenarimol, piperalin and QBAs tank mix, and a water control, with subsequent applications at (**A**) 6 and 24 d after treatment during Dec. 1996 or (**B**) 7 and 17 d during Jan. 1997, on percentage of reduction of *Sphaerotheca pannosa* var. *rosae* (powdery mildew) infection on greenhouse roses. Each mean represents 32 observations from the four cultivars ('Gabriella', 'Royalty', 'Samantha', and 'Sonia') pooled. Vertical bars represent least significant differences at $P \leq 0.05$.

for eradicant and long-term control of powdery mildew (Powell, 1998). Considering this, and the fact that the QBA formulation was not as immediately effective in eradicating powdery mildew as piperalin, but had a longer efficacy, a series of "tank mix" trials were conducted. During the 1996–97 studies, initially, 3 to 6 d after application, all single-fungicide formulations performed as in the earlier trial (Fig. 3A). During the Dec. 1996 trial, the QBA/piperalin tank mix was more effective than the single formulations, but after the second and third applications, the tank mix was no more effective than was copper sulfate pentahydrate or piperalin; however, it was more effective than QBA or fenarimol alone (Fig. 3A). During the Jan. 1997 trial, the QBA/piperalin tank mix controlled powdery mildew more effectively than did QBA alone, and was as effective as piperalin, fenarimol, or copper sulfate pentahydrate 3 or 6 d after application (Fig. 3B). Two weeks after the initial application the QBA/piperalin tank mix remained as effective as copper sulfate pentahydrate, and these treatments were more effective than the other fungicides until after a third application (Fig. 3B).

The enhanced control of powdery mildew by the QBA/piperalin tank mix can probably be attributed to piperalin as an eradicant, which gives good immediate mildew control, and QBA as a more slowly effective fungicide, which extends mildew control over a longer period. This combination may allow a rose grower to reduce the frequency of pesticide applications. No tank mixes of copper sulfate pentahydrate with QBA were evaluated because the former has a 24-h restricted interval for worker reentry (Powell, 1998), which makes it an undesirable pesticide in a rose greenhouse. Piperalin and fenarimol have a 12-h restricted interval and are both commonly used by rose growers. The QBA product used in this experiment, as currently formulated, should qualify for a 12-h, and possibly 4-h, restricted entry interval, which will make it an attractive new product for rose growers.

Expt. 5. To this point, all of the QBA trials were conducted at Colorado State Univ. For final verification of efficacy, trials were conducted at two commercial rose greenhouses using a series of QBA rates. Even though the greenhouses differed in glazing, environment, location, and cultivars, the results were similar at both; thus, the data were pooled for statistical analysis. Eight days after application, even the lowest rate (12.5 $mg \cdot L^{-1}$) was effective in controlling powdery mildew (Fig. 4); however, the 38 and 50 $mg \cdot L^{-1}$ rates yielded the most consistent control. The rose grower's observations at each location provided additional confirmation of the relative degree of control.

The QBA formulation was effective in eradicating and controlling *Sphaerotheca pannosa* var. *rosae*. Quaternary benzophenanthridine alkaloids extracted from *Macleaya cordata* have the potential to provide the active ingredient for an effective biorational pesticide for the greenhouse rose industry, equal to or better than some of the fungicides currently used.

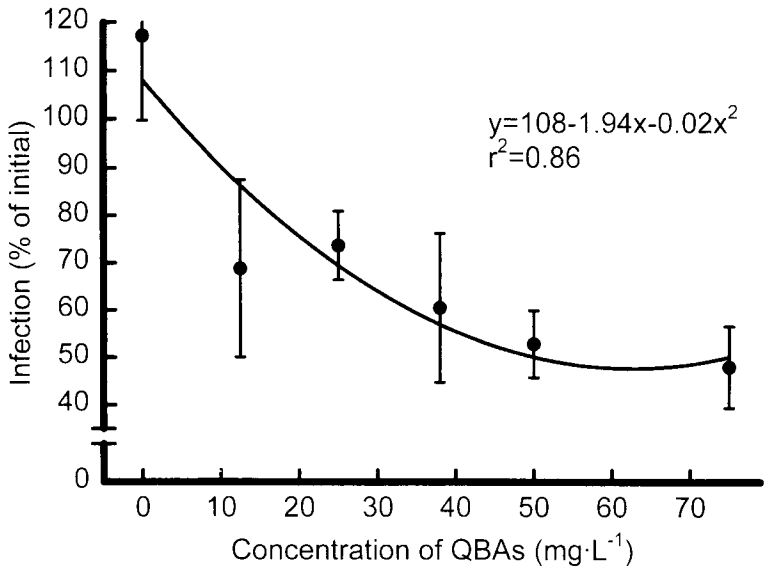

Fig. 4. Efficacy of quaternary benzylphananthridine alkaloids (QBAs) 8 d after application to greenhouse roses (cultivars Gabriella and Royalty) for control of *Sphaerotheca pannosa* var. *rosae* (powdery mildew) infection in commercial greenhouses during Sept. 1997. Each point is the mean of total of 16 observations from the two cultivars and sites pooled. Vertical bars represent least significant differences at $P \leq 0.05$.

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QWEL®

Material Safety Data Sheet

Transportation and Medical Emergency Phone: 800-535-5053

General Phone: 970-223-7260

EPA Registration Number 69876-1
Effective Date: April 29, 2003

QWEL® (CTI 13-19B) Liquid Concentrate

Camas Technologies, Inc., Broomfield CO

NOTICE: The information set forth herein is offered as a service to our customers and is not intended to relieve a customer from its responsibility to determine the suitability of this information or of the materials described herein for the purchaser's purposes to investigate other sources of information, to comply with all laws and procedures regarding safe use of these materials; and to use these materials in a safe manner. Although this information is believed to be accurate, Camas Technologies, Inc. specifically disclaims responsibility for any inaccuracy set forth herein.

Section I –Product Identification

Product	QWEL® (CTI 13-19B) Liquid Concentrate 1 Quart and 1 Gallon
EPA Registration Number:	68976-1
DOT Proper Shipping Name:	Alcohol N.O.S. (Methyl Alcohol 18%)
DOT ID Number:	UN 154
DOT Label:	Flammable Liquid

Section II- Hazardous Ingredients/Identity Information

Chemical Name	CAS Number	Concentration
Methanol	67-56-1	18%
Macleaya Extract	112025-60-2	1.5%

Section III – Physical/Chemical Characteristics

Boiling Point 65 °C	Specific Gravity 0.99 g/mL
Melting Point NA	Evaporation Rate NA
Vapor Pressure NA	Vapor Density NA
Appearance Liquid	Odor None
Color Orange	Solubility in Water Very Soluble

NA = Not Applicable

Section IV – Fire and Explosion Hazard Data

Flash Point (Closed Cup) 36°C
Autoignition Temperature Not Applicable
Extinguishing Media: Dry Chemical or Carbon Dioxide
Special Fire Fighting Procedures Use self-contained breathing apparatus
Unusual Fire and Explosion Hazards Not Applicable

Section V – Reactivity

Stability: Stable Do not Store near heat or flame
Hazardous Decomposition Products: May give off Carbon Dioxide when burned
Hazardous Polymerization: Not known to occur

Section VI- Health Hazard

EYE: May cause severe irritation with corneal injury and permanent impairment
SKIN: Does not cause skin irritation and does not cause allergic skin reactions LD_{50} >2000 mg/L in rabbits
INGESTION: Single Oral Dose Toxicity is low 1544mg/Kg for males and 960 mg/Kg for females
INHALATION: Toxicity is low for this product
TERATOLOGY: Not known to be a teratogen in laboratory animals
CARCINOGENICITY: Not known to be a carcinogen in laboratory animals
REPRODUCTION: Not known to affect reproduction or fertility in laboratory animals
MUTAGENICITY: In –vitro and animal mutagenicity studies were negative

Section VII-Accidental Release Measures

In case of a spill use absorbent materials to contain and clean up small spills and dispose as waste. Report spills and contact Camas Technologies for assistance. Do not use hot or sparking equipment in the immediate area and contain spill from runoff.

Section VIII- Environmental Information

This product is toxic to fish. Do not apply directly to water, to areas where surface water is present. Drift and runoff from treated areas may be hazardous to aquatic organism. Do mot apply when weather conditions may cause runoff or drift from the target area. Do not contaminate water when disposing of equipment wash or rinse.

Section IX-Personal Protection

Eye Protection: Use chemical goggles. Eye wash fountain should be located in immediate work area

Skin Protection: Use protective clothing which protects from this material. Selection of specific items such as faceshield, gloves, boots apron or full body suit will depend on operation.

Section X- Disposal Considerations

Do not contaminate food, feed, or water by storage or disposal. Pesticide wastes are considered toxic. Improper disposal or excess pesticide spray mixture is a violation of federal law. If wastes resulting from the use of this product cannot be disposed of according to label instructions, dispose of the waster at an approved facility or contact your state pesticide or environmental control agency disposal. Contact the hazardous waste representative at the nearest EPA regional office for guidance.

Section XI- Toxic Substances Control Act (TSCA)

All ingredients are on the TSCA inventory or are not required to be listed on the TSCA inventory.

United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: Macleaya Extract
Reason for Issuance: New Chemical
Date Issued: September 19, 2002

Description of Chemical

Chemical Name:	Active components are: Sanguinarine chloride: [1,3] benzodioxolo [5,6-c] phenanthridinium-13-methyl chloride and Chelerythrine chloride: [1,3] benzodioxolo [5,6-c] phenanthridinium-1,2-dimethoxy-12-methyl chloride.
Common Name:	Macleaya Extract
Trade Name:	Qwel (CTI 13-19B) Liquid Concentrate
Chemical Class:	Quaternary benzophenanthridine alkaloids (QBA)
EPA Chemical Code:	069095
Chemical Abstracts Service (CAS) Number:	112025-60-2
Year of Initial Registration:	2002
Pesticide Type:	Fungicide
U.S. Producer:	Camas Technologies, Inc. P.O. Box1357 Broomfield, CO 80038

Use Pattern and Formulations

Qwel (CTI 13-19B) Liquid Concentrate is a liquid product containing 1.5% of the active ingredient (ai) macleaya extract (0.125 lb ai/gallon). Qwel is applied as a spray mist for the control of powdery mildew and Alternaria and Septoria leafspots on a variety of ornamental plants in enclosed commercial greenhouses. Dosage rates vary from 3 to 5 fl.oz./10 gallons water applied to 2,000 sq. ft. for small plants or 1,250 to1,500 sq. ft. for roses and other larger plants. Applications are repeated at 8 -10 day intervals.

Science Findings

Summary Science Statement

EPA has concluded from the review of the supporting data that there are no risks of concern from the use of macleaya extract. The end-use product is in Toxicity Category I because of primary eye irritation concerns. Based upon the use pattern for this product, the only toxicological concern would be related to worker exposure. Risk from exposure of workers (applicators and other handlers) was below the Agency's level of concern. No food uses are proposed for the product so there would be no dietary exposure. Additionally, since the product will be used in enclosed greenhouses, there would be no exposure through drinking water. The product will not be registered for residential or homeowner uses so there would be no non-occupational exposure expected, including exposure of infants or children. The Agency concluded that the use of macleaya extract on the labeled ornamental plants in enclosed greenhouses is unlikely to present a significant threat to non-target organisms or the environment.

Physical/Chemical Properties

Physical and Chemical Properties for Technical Grade Active Ingredient	
Requirement	**Result or Deficiency**
Color	Orange
Physical State	Free-flowing powder
Odor	Nasal irritant
Storage Stability	Greater than one year
Corrosion Characteristics	Non-corrosive
pH	3.29 (1.0% solution)
Melting Point/ Melting Range	237-258° C

Physical and Chemical Properties for Technical Grade Active Ingredient	
Requirement	**Result or Deficiency**
Density/ Relative Density/ Bulk Density	0.43 g/ml
Solubility	Water: 1.2% (w/v) Methanol: 2.5% (w/v) Toluene: <0.002% Acetone: <0.002%

Toxicity Profile:

81-1	Acute Oral	44525106	Males:= 1016 mg/kg in corn oil); 1544 mg/kg (CMC) Females:= 629 mg/kg in corn oil; 960 mg/kg (CMC)	III
81-2	Acute Dermal - rabbit	44525107	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	44525108	**Males:**< 0.22 mg/L **Females**:> 0.22 mg/L and < 0.52 mg/L	II
81-4	Primary Eye Irritation	-	Not conducted	-
81-5	Primary Skin Irritation	-	Not conducted	-
81-6	Dermal Sensitization	-	Not conducted	N/A

Toxicity Studies other than Acute Toxicity:

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3100 **13-Week feeding - rat** **(Sanguinaria Extract: (44.5% sanguinarine chloride and 78.6% alkaloid))**	45400502 1987/Unacceptable guideline 0, 50, 100, 200, 300, or 400 mg/kg/day by gavage (20 mL/kg)	**NOAEL**: Not established **LOAEL**: 50 mg/kg/day (decreased overall body weight gain, labored breathing and rales in both sexes (LDT)).

Toxicity Studies other than Acute Toxicity:

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3100 13-Week feeding - monkey (Sanguinarine Chloride (98.8% a.i.)	45400504 1988/Acceptable guideline 0, 10, 30, or 60 mg/kg bw/day by gavage (2.0 mL/kg)	**NOAEL**: Not established **LOAEL**: 10 mg/kg/day (increased incidence (number of affected animals) and frequency of emesis and diarrhea in both sexes (LDT)).
870.3700 Developmental toxicity - rat (Sanguinaria extract (33% sanguinarine chloride and ~68% total benzophenanthridine alkaloid))	44525111 1989/Acceptable nonguideline 0, 5, 20, and 60 mg/kg/day by gavage (10 mL/kg) From literature	**Maternal NOAEL**: 20 mg/kg/day **Maternal LOAEL**: 60 mg/kg bw/day (reduced weight gain) **Developmental NOAEL**:Greater than 60 mg/kg/day (HDT) **Developmental LOAEL**: Could not be established.
870.3700 Developmental toxicity - rabbit (Sanguinaria extract (33% sanguinarine chloride and ~68% total benzophenanthridine alkaloid))	44525111 1989/Acceptable nonguideline 0, 5, 15, 25, 50, and 75 mg/kg/day by gavage (4 mL/kg) From literature	**Maternal NOAEL**: 15 mg/kg/day **Maternal LOAEL**: 25 mg/kg/day (clinical signs of toxicity and weight loss mg/kg/day). **Developmental NOAEL**: 25 mg/kg/day **Developmental LOAEL**: 50 mg/kg/day (decreased number of fetuses/litter and increased postimplantation loss).
870.3800 1-Generation Reproduction - rat (Sanguinaria extract (33% sanguinarine chloride and ~68% total benzophenanthridine alkaloid))	44525111 1989/Acceptable nonguideline 0, 10, 30, or 100 mg/kg/day by gavage (10 mL/kg) From literature	**Parental NOAEL**: 10 mg/kg/day **Parental LOAEL**: 30 mg/kg bw/day (clinical signs indicative of central nervous system toxicity) **Offspring NOAEL**: 30 mg/kg/day **Offspring LOAEL**: 100 mg/kg bw/day (decreased body weight of pups at birth and during lactation) **Reproductive NOAEL**: Greater than 100 mg/kg/day (HDT) **Reproductive LOAEL**: Could not be established.
870.4300 Chronic/Carcinogenicity - rat (Sanguinaria Extract (purity not reported)	45400505 1989/Unacceptable guideline 0, 5, 20, or 60 mg/kg/day by gavage (10 mL/kg)	**NOAEL**: 20 mg/kg/day **LOAEL**: 60 mg/kg/day based on decreased overall body weight gain in females and increased salivation and rales in both sexes Not oncogenic under conditions of study

Summary of Toxicology Findings.

The Agency has not selected acute or chronic reference doses (RfDs) because there are no proposed food uses for macleaya extract. For this same reason, the potential for increased susceptibility of infants and children from exposure to macleaya extract was not evaluated. Incidental oral endpoints are not applicable because there are no residential uses. Neither a

dermal absorption study nor a dermal study was available so a default dermal absorption value of 100% was applied.

Macleaya extract is a botanical extract of *Macleaya spp.* In support of registration, studies conducted with sanguinaria extract, a product closely related to macleaya extract and sanguinarine chloride, a major component of macleaya extract have been submitted. Macleaya extract contains approximately 47-53% sanguinarine and 20-26% chelerythrine whereas sanguinaria extract contains approximately 37-40% sanguinarine, 16-18% chelerythrine, and other related products ranging from less than 1% to 9% of the total composition.

Acute Toxicity

The data for macleaya extract indicate that the acute oral toxicity and acute dermal toxicity values are in toxicity category III and that acute inhalation toxicity is in toxicity category II. The end-use product, Qwel (CTI 13-19B) Liquid Concentrate, containing 1.5% macleaya extract, is in toxicity category I for primary eye irritation, toxicity category III for acute oral and acute dermal toxicity, and in toxicity category IV for acute inhalation and primary dermal irritation. A repeated insult patch test on humans was submitted which indicated that the product is negative for sensitization. The test was non-guideline but is acceptable for regulatory purposes.

Dermal Exposure

To evaluate potential risks associated with dermal exposure across all durations of exposure, an endpoint was selected from a 1-generation reproduction and fertility effects study in rats. In this study, sanguinaria extract was administered by gavage to groups of 10 male and 20 female rats at doses of 0, 10, 30 or 100 mg/kg/day. The parental systemic LOAEL for sanguinaria extract is 30 mg/kg/day for F_0 male and female rats based on clinical signs indicative of central nervous system toxicity; the corresponding NOAEL is 10 mg/kg/day. Mortality, more severe clinical signs, and reduced weight gain occurred at 100 mg/kg/day. The offspring LOAEL for sanguinaria extract in rats is 100 mg/kg/day, based on decreased body weight of pups at birth and during lactation; the corresponding offspring NOAEL is 30 mg/kg/day. The reproductive NOAEL is 100 mg/kg/day (HDT). A reproductive LOAEL was not established in the study.

The dose and endpoint selected for risk assessment from dermal exposure is 10 mg/kg/day based on one or more of the following clinical signs at the parental LOAEL of 30 mg/kg/day: breathing difficulty, signs of lethargy, reduced motor activity, intermittent head twitching, and excessive salivation.

Inhalation Exposure

To evaluate the potential risks associated with inhalation exposure across all durations of exposure, the Agency selected an endpoint from a 90-day oral toxicity study in monkeys. In this study, sanguinarine chloride was administered to 4 cynomolgus monkeys/sex/dose via gavage at

dose levels of 0, 10, 30 or 60 mg/kg/day. The LOAEL for this study is 10 mg/kg/day based on increased incidence (number of affected animals) and frequency of emesis and diarrhea in both sexes. The NOAEL was not observed.

The dose/endpoint selected for risk assessment for inhalation exposure is10 mg/kg/day based on increased incidence and frequency of emesis and diarrhea in the males and females. The 90-day monkey study was selected for the inhalation endpoints because of the possibility that the effects were partially due to the irritating properties of the chemical, which could translate to irritation effects in the lung. Although this study was conducted with sanguinarine chloride, it is not likely to underestimate any potential risks observed with macleaya extract because the effects are observed at a dose where no effects are observed with sanguinaria extract, which is very similar to macleaya extract. An additional uncertainty factor of 3 will be used for lack of a NOAEL.

Carcinogenicity

Carcinogenicity studies are generally not required for indoor, non-food uses. The following data were submitted for informational purposes.

In a combined chronic toxicity/carcinogenicity study, sanguinaria extract (purity not reported; Lot #: H15 Sept 86-64) in 1% aqueous citric acid was administered daily by gavage for 91/99 weeks (males/females) to 50 rats/sex/dose at doses of 0, 5, 20, or 60 mg/kg/day. The LOAEL is 60 mg/kg/day based on decreased overall body weight gain in females and increased salivation and rales in both sexes. The NOAEL for this study was 20 mg/kg/day. At the doses tested, no treatment-related increase in the incidence in any type of tumor was observed when compared to the control groups. Dosing was considered minimally adequate based on decreased overall body weight gain in females and increased salivation and rales in both sexes. Although the observed effects in the lung and trachea were not significant enough to use as the basis for the LOAEL, it is likely that these effects were due to a combination of the route of administration (gavage) and the irritating properties of the chemical. Because of this, higher doses may have caused more severe problems.

The oncogenicity portion of the study is unacceptable/guideline, not upgradable and does not satisfy the guideline for a carcinogenicity study (OPPTS 870.4200; OECD 451) in rats. Excessive mortality, including in the control groups, prevented the 104 week duration of observation for the study. In addition, there were a significant number of gavage errors. For the chronic toxicity portion of the study, a significant number of guideline measurements were not performed. These included ophthalmology, clinical chemistry, urinalysis, and organ weight determinations. In addition, the purity of the sanguinaria extract was not reported. This was indicated for the subchronic oral study. Without the purity, it is difficult to compare the observed toxicity of the extract in the two studies. The chronic portion of the study is classified as unacceptable/guideline, not upgradable and does not satisfy the guideline requirement for a chronic study in rodents (OPPTS 870.4100; OECD 452). However, some of the data may be useful for regulatory purposes.

Mutagenicity

No actual mutagenicity studies are available but there is a literature review. The summary from the literature review states: "Sanguinaria extract and sanguinarine chloride were tested for mutagenic potential in a series of assays using bacterial, mammalian cell culture, and mouse DNA systems. Sanguinaria extract and sanguinarine chloride elicited weak positive responses only in the bacterial assay using *Salmonella typhimurium* (Ames assay) in the presence of metabolic activation. Studies of Sanguinaria extract were negative in the bacterial assay with *E. coli*, in an unscheduled DNA synthesis assay in rat primary hepatocytes and in a micronucleus cytogenetic assay in mice. An Ames test for metabolites of Sanguinaria extract in rat urine using *S. typhimurium* was negative. Studies of sanguinarine chloride were negative in a second Ames assay with *S. typhimurium* and *Saccharomyces cerevisiae* with and without metabolic activation. Two mammalian cell assays with sanguinarine chloride, including a Chinese hamster ovary (CHO) - HGPRT forward gene mutation assay and unscheduled DNA synthesis assay in rat primary hepatocytes, provided results that were equivocal or uninterpretable; neither study, however, gave a positive mutagenic response. The Panel noted that the CHO assay is historically difficult to conduct and interpret."

Occupational Exposure and Risk Characterization

Handlers (Commercial)

Macleaya extract is the active ingredient (1.5%) in the product Qwel ™ (CTI 13-19B). It is an ornamental plant fungicide to be used in enclosed commercial greenhouses to control powdery mildews and leafspot. Macleaya will be applied as a foliar spray by backpack or high pressure sprayer. The application rate is 0.0005 lb a.i. per gallon. Foliar applications may be made at 8-10 day intervals as needed. The formulation is a liquid concentrate.

Workers may be exposed to macleaya extract during mixing, loading, and application activities. Based on the proposed application rates and use scenarios, short- , intermediate- and long-term dermal and inhalation exposure is expected. The exposure scenarios assessed are: mixing/loading and applying liquid for backpack and mixing/loading and applying liquid for high pressure sprayer.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted to the Agency in support of this application. It is the policy of the Agency to use data from the Pesticide Handler Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure, Policy 007, "Use of Values from the Pesticide Programs," January 1999).

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has

developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. The Agency has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments.

The MOEs calculated for liquid application with high pressure handwand are 400 for dermal with baseline PPE, 560 for dermal with minimum PPE and 12,000 for inhalation with baseline PPE. Liquid applications with backpack sprayer had MOEs of 14,000 for dermal with minimum PPE and 1,200,000 for inhalation with baseline PPE. The handler MOEs for dermal exposure were greater than 100 and the inhalation exposures were greater than 300 and therefore did not exceed the Agency's level of concern. The baseline clothing/PPE level scenario for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves and no respirator.

The handler exposure estimates in this assessment are based on using maximum application rate, and are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence) and assumptions regarding the amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates based on 100% dermal absorption and professional experience and judgement.

Post-Application Exposure

Due to the fact that greenhouse workers are exposed to this fungicide on a continuous basis during post-application activities (cut/harvest, prune, sort and pack), chronic (6 or more months of continuous exposure) post-application dermal and inhalation exposure is expected. Since no post-application data were submitted in support of this registration action, exposures during post-application activities were estimated using dermal transfer coefficients from the Science Advisory Council For Exposure Policy Number 3.1: Agricultural Transfer Coefficients, August 2000.

The MOEs calculated for post-application activities are: 110 for hand harvest and pruning, pinching, and thinning; 2,000 for just harvesting and 4,500 for hand pinching. The post-application MOEs were greater than 100 and did not exceed the Agency's level of concern. Input parameters such as the dissipation rate and transfer coefficients are considered to be high-end, while estimates of the exposure duration and body weight are central tendency estimates.

Additional Toxicity Data Requirements

The data requirements for Macleaya Extract will follow the requirements for a non-food use chemical (40 CFR 158.340) as follows:

Primary eye irritation (870.2400), primary dermal irritation (870.2500) and dermal sensitization (870.2600) studies: data are available on the formulation but not on the technical material. These data are required in order to evaluate the requested re-entry interval of 4 hours. In the interim, a 12-hour REI will be required.

90-Day Dermal Study in the Rabbit (§870.3250): There are concerns for toxicity to workers from dermal exposure. Long-term dermal exposure is anticipated. Based on an examination of the data, the rabbit appears to be the most sensitive species. Therefore, a dermal study on the rabbit is required using macleaya extract. No dermal studies are currently available for macleaya extract. An oral study on sanguinaria extract has been selected to provide a preliminary estimate for the dermal risk assessment. This oral study is considered to be sufficient for a preliminary risk estimate because the default assumption of 100% dermal absorption is considered to be very conservative and is anticipated not to underestimate any potential risk via the dermal route.

90-Day Inhalation Study in Rats (§870.3465): There are concerns for toxicity to workers from inhalation exposure. Long-term inhalation exposure is anticipated. Since this chemical appears to be an irritant via the oral route, toxic effects are anticipated via inhalation exposure. Therefore, in order to more fully characterize these effects, an inhalation study is required.

Developmental study in the rabbit (§870.3700): A literature article summarizing developmental studies in the rat and rabbit and a 1-generation reproduction study in the rat is available for sanguinaria extract. The article indicates that the rabbit is likely to be the most sensitive species for macleaya extract. The literature article does not provide sufficient data to fully assess developmental toxicity, particularly as it relates to the disposition of the does in the rabbit study (i.e. deaths, pregnancy rates, etc.). Individual animal data are needed. Since these data are not available, the literature study is classified as Non-guideline. Insufficient litters were available in the rabbit study for a complete assessment. Therefore, we are requesting the rabbit as the choice of species to satisfy the requirement for a developmental toxicity study in one species.

Mutagenicity battery (gene mutation in bacteria (Ames; 870.5265)) and mammalian cells (870.5300) and an *in vivo* cytogenetics assay (870.5380, .5385, or .5395)): Although mutagenicity studies have been previously conducted with sanguinarine chloride, the data for these studies are not available to the Agency for review. Summaries of the data are published but the data upon which the summaries are based were destroyed in a fire. Mutagenicity studies are required for a non-food use chemical.

Ecological Effects and Environmental Fate Characteristics

Ecological Toxicity Data. The following toxicity data are available and fulfill the ecological effects data requirements for an indoor use:

1. In an acute oral study on rats using the technical grade active ingredient (TGAI), the acute

oral LD_{50} was 845 and 1216 mg/kg/day which is considered slightly toxic.

2. In a test with the TGAI fed to bobwhite quail, the dietary LC_{50} was >3946 ppm. The maximum concentration did not yield an LC_{50} and did not go up to 5000 ppm so the toxicity category could not be determined but was no worse than slightly toxic.

3. In a test on rainbow trout using the TGAI, the 96-hour LC_{50} was 89 ppb which is considered to be very highly toxic.

4. In a test with *Daphnia magna* using TGAI, the 48-hour EC_{50} was 20 ppb which is considered to be very highly toxic.

Environmental Fate Data

The registrant did not submit environmental fate data for this product. Indoor use products usually require hydrolysis, aerobic soil metabolism and leaching and adsorption/desorption studies. Based on the use pattern for this product, these studies are waived since it is assumed that this chemical will not get outdoors while being used and there is little likelihood that the mobility, persistence and degradate information obtained from these studies would be used to characterize exposure or risk.

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