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^{o} 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:

Acute Toxicity Profile of Macleaya Extract				
GDLN	**Study Type**	**MRID**	**Results**	**Tox Category**
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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