Aminoethoxyvinylglycine hydrochloride (aviglycine HCl), formerly designated as aminoethoxyvinylglycine (AVG) (129104) Fact Sheet

I. Description of the Chemical

Generic Name(s) of the Active Ingredient:

Aminoethoxyvinylglycine (AVG);
L-alpha-(2-aminoethoxyvinyl)glycine hydrochloride;
[S]-trans-2-amino-4-[2-aminoethoxy]-3-butenoic acid hydrochloride

OPP Chemical Code (CAS #) : 129104 (55720-26-8)

Year of Initial Registration: 1997

Pesticide Type: Biochemical plant regulator

Registrant (2001):

Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60148

II. Use Sites Uses, and Application

- **Use Sites and uses:** Aminoethoxyvinylglycine (AVG) is a plant regulator used on apples, pears, and ornamentals. In apples, it may delay fruit maturity, leading to benefits such as a reduction in pre-harvest fruit drop and improved fruit quality. In pears, AVG may help maintain fruit firmness. For specific ornamentals (miniature carnations, hibiscus, and rooted geranium cuttings and seedlings), AVG may reduce problems, such as flower senescence and flower bud abscission, that occur during shipping.

- **Application:** AVG to be used as a spray solution, applied to apples or pears as a single application 28 days prior to the anticipated beginning of the normal harvest period, and to specified ornamentals 24-to -48 hours prior to boxing/shipping.

III. Science Findings

A. Toxicology

All toxicity data requirements have been satisfied for the purpose of the conditional registration. The information submitted to support the acute toxicity requirements for AVG indicate toxicity category IV (virtually not toxic, i.e., the lowest toxicity category on a scale from I-IV) for acute oral toxicity, primary eye irritation, and primary dermal irritation. AVG is category III (slightly toxic) for acute dermal toxicity and acute inhalation toxicity. The chemical is not a dermal sensitizer.

B. Human Health Effects

No unreasonable adverse effects to human health are expected from the use of AVG.

1. Risks Posed by Potential Dietary Exposure

Because the *Streptomyces* bacterial species that produces AVG is soil-borne, the general human population may be exposed to naturally occurring AVG. Pesticidal use may increase exposure compared with that from natural levels. Based on data from acute toxicity/pathogenicity studies, along with the associated time-limited tolerances (maximum concentration of pesticide residue permitted to be present on or in food), the Agency concludes that there is no significant risk from dietary exposure.

2. Effects on Immune and Endocrine Systems

The technical grade active ingredient caused immunosuppression in the rat. Absolute (49%) and relative (41%) thymus weights decreased significantly ($p \leq 0.05$) in the high dose group. The primary antibody response to sheep red blood cells (SRBC), measured by the mean number of anti-SRBC plaque-forming cells (PFCs) per spleen and per 10^6 viable spleen cells, decreased significantly ($p \leq 0.05$) at the end of the treatment period by 90% and 87%, respectively. The anti-SRBC response and thymus weight suppression was reversible in a 28-day recovery group of rats. Since the no observed effect level (NOEL) of 5 mg/kg/day in this study was higher than in the study used for reference dose (RfD) determination (1.77 mg/kg/day), the conclusions of no significant risk based on a 1000-fold safety factor for

the proposed uses and exposure are not affected by the results of this study.

Available subchronic and developmental toxicity data do not indicate that AVG has any endocrine effects. EPA is currently in the process of determining how it will address estrogenic and thyroid effects from pesticide residues in general.

3. **Risks Posed by Potential Residential, School or Daycare Exposure**

No residential, school or daycare uses currently appear on the labels. The use sites are all agricultural for use as a plant regulator on growing plants. Therefore, non dietary exposure to these sites where children are present is minimal to nonexistent.

4. **Potential for the Transfer of the Pesticide to Drinking Water**

In examining aggregate exposure, the Food Quality Protection Act (FQPA) directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

Because the Agency lacks sufficient water-related exposure data to complete a comprehensive drinking water risk assessment for many pesticides, EPA has commenced and nearly completed a process to identify a reasonable yet conservative bounding figure for the potential contribution of water-related exposure to the aggregate risk posed by a pesticide. In developing the bounding figure, EPA estimated residue levels in water for a number of specific pesticides using various data sources. The Agency then applied the estimated residue levels, in conjunction with appropriate toxicological endpoints (RfDs or acute dietary NOELs) and assumptions about body weight and consumption, to calculate, for each pesticide, the increment of aggregate risk contributed by consumption of contaminated water. While EPA has not yet pinpointed the appropriate bounding figure for consumption of contaminated water, the ranges the Agency is continuing to examine are all below the level that would cause AVG to exceed the RfD by the time-limited tolerances which have been granted for this pesticide. The Agency therefore concluded that the potential exposures associated with AVG in water, even at the higher levels the Agency is considering as a

conservative upper bound, would not prevent the Agency from determining that there is a reasonable certainty of no harm, as required by FQPA.

5. **Acute and Chronic Dietary Risks for Sensitive Subpopulations, Particularly Infants and Children**

A dietary risk evaluation was performed using the RfD of 0.002 mg/kg/day and the Theoretical Maximum Residue Contribution (TMRC) as a worst-case scenario. The results from the Tolerance Assessment System Routine Chronic Analysis dated February 3, 1997 show:

Subpopulation	**Percent of RfD**
Nursing infants (<1 year old)	27.59
Non-nursing infants (<1 year old)	36.11
Children (1-6 years old)	11.19
Children (7-12 years old)	04.62
Males (13-19 years old)	02.12
Females (13-19 years old; non-pregnant, non-nursing)	2.11
Nursing females (13+ years old)	3.00
Pregnant females (13+ years old)	2.03

The percent of the RfD that will be utilized by the aggregate exposure to AVG will range from 4.6% for children 7-12 years old, up to 36.1% for non-nursing infants less than one year old. Because the RfD was based on a developmental study with a 1000-fold safety factor, infants potentially exposed at 36.1% RfD have an adequate margin of safety. A dietary risk evaluation based on Anticipated Residue Contribution (ARC) may indicate a lower dietary exposure to aminoethoxyvinylglycine. Based on available data, EPA concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure.

6. **Cumulative Exposure From Multiple Routes Including Dermal, Inhalation, and Oral Exposure**

EPA does not have, at this time, available data to determine whether AVG has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other

pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, AVG does not appear to generate a toxic metabolite that is also produced by other substances. Therefore, EPA has not assumed that AVG has a common mechanism of toxicity with other substances. Based on the exposure and toxicity assessments described below, EPA finds no significant risk to human health as long as users follow label precautions, including use of Personal Protective Equipment.

Exposure to the agricultural-use end products will be primarily to mixer/loaders and applicators, occurring outdoors or in greenhouses. Exposure to others is expected to be minimal to nonexistent.

Skin and lungs would be the primary routes of exposure for mixers/loaders and applicators. In a 21-day repeated dose dermal toxicity study in rodents, the test compound caused no treatment-related signs of toxicity. No significant acute inhalation toxicity was observed in rodent studies with the TGAI (Technical Grade Active Ingredient) or the 15% end-use product. Thus, the risks anticipated for these routes of exposure are minimal. Oral exposure to AVG is possible through consumers eating treated produce.

Comparisons of the exposure estimates to the NOELs for maternal and developmental toxicity (using the value of 1.77 mg/kg/day for maternal and developmental toxicity), indicate unacceptable Margins of Exposure (MOEs) for mixer/loaders and air blast applicators wearing long pants, long-sleeved shirts and no gloves, and for greenhouse handgun applicators wearing long pants and long-sleeved shirts, with or without gloves.

These MOEs were calculated based on the most sensitive individual, a pregnant female, and thus the NOEL from the developmental toxicity study was used. However, the developmental toxicity study was based on oral exposure to the TGAI. The results of the 21-day repeated dose dermal toxicity study, in which no toxicity was observed at the highest dose tested (1000 mg a.i./kg/day), along with the results of the acute inhalation toxicity studies, mitigate concern over the dermal and inhalation risk of worker exposure to AVG.

End-use product labels require Personal Protection Equipment and a Restricted-Entry Interval of 12 hours to meet the Agency's Worker Protection Standard.

C. Ecological Effects

AVG is practically nontoxic to freshwater fish and freshwater invertebrates, and is not expected to cause adverse effects to these organisms.

AVG is moderately toxic to northern bobwhite, a result that indicates that the biochemical may cause adverse effects to exposed birds. Although the biochemical is naturally occurring, the results of acute toxicity (Tier I) bird tests triggered the need for additional testing. The registrant submitted a terrestrial risk assessment, which suggested that AVG is not expected to pose an unreasonable risk to bird species if users follow label directions. However, due to possible exceptions, some products are required to carry the following language: "This pesticide is moderately toxic to avian species and exposure to birds should be avoided."

Risk to mammalian wildlife is expected to be minimal to nonexistent.

No significant toxicity to non target plants is expected from the use of AVG under the proposed use pattern.

Non target insect or honeybee studies were not required for these products due to a limited possibility of exposure from the use pattern. However, food-use end-product labels must clearly state that application of product may occur only after fruit set, when there would be no flowers to attract these insects.

It has been concluded from the data submitted that there would not be a "may affect" situation for endangered mammals, plants, insects and aquatic species from the proposed use of the products. Provided that the end-use products for use in apple and pear orchards are applied in accordance with label directions, no unreasonable risk to endangered birds is expected.

IV. Public Interest Finding

EPA determined in the Public Interest Finding that conditional registration of an end-use product allowing application to apples would be in the public interest. Pears and ornamentals are minor crops which do not require analysis to qualify for a conditional registration.

EPA reviewed the test information submitted by the registrant and concurred with the claim that application of AVG to apples would increase the quality of fruit at packout. A portion of the increased quality fruit would be marketed as fresh market apples instead of processed, and some would be of larger size or exhibit other quality improvements. These

characteristics increase the market price to the grower, other things equal. However, a significant increase in the quantities of fresh market and higher grade apples would result in market price adjustments for apples where the consumer would obtain benefits in terms of lower price as well as more apples of higher quality. This means the grower, and possibly the registrant, would receive lower monetary returns than projected by the registrant.

V. Summary of Data Gaps

The original 1997 registrations were conditional pending a) the submission and review of a two-generation rat reproduction study, and b) validation by an EPA laboratory of the submitted analytic enforcement method. The expiration date of April 1, 2001 allotted four years for submission and review of the data and validation of the analytic enforcement method. The analytical method was subsequently validated and provided to the Food and Drug Administration, and the registrant submitted the conditional data on September 27, 1999, in advance of the deadline.

The 2001 AVG registrations are also conditional. A data gap currently exists for the rat two-generation reproduction study because the Agency has not concluded its assessment of the data. All tolerances are time-limited, to expire on December 21, 2003, because of this data gap. The time limitation allows for review of the data. Based on the available toxicological data, the 1000-fold uncertainty factor, and the levels of exposure, the EPA has determined that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to the pesticide AVG and its residues during the period of the time-limited tolerances.

VI. Regulatory Timeline

April 28, 1997 Conditional registrations issued for first pesticide products containing AVG. Four years were allotted for submission of additional data and EPA lab validation of the analytic enforcement method (expiration date of April 1, 2001).

May 7, 1997 Establishment of time-limited tolerances of 0.08 part per million for residues of AVG in or on apples and pears (expiration/revocation date of April 1, 2001).

July 2, 2001 Conditional registrations issued for pesticide products containing AVG (expiration date of December 21, 2003).

July 12, 2001 Establishment of time-limited tolerances of 0.08 part per million for residues of AVG in or on apples and pears (expiration/revocation date of December 21, 2003)

As of November 2001, AVG was registered for use in 3 end-products and one technical product.

VII. Additional Contact Information

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