Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 4.1 Application

Application Numbers: 2007-4210, 2007-4235
Application: Conversion to full registration without consultation
Products: Retain Technical Powder, Retain Plant Growth Regulator
Registration Number: 25608, 25609
Active ingredients (a.i.): Aviglycine hydrochloride
PMRA Document Number : **1874752**

Purpose of Application

The purpose of this application was to convert the technical product, Retain Technical Powder (Registration Number 25608), and the associated end-use product, Retain Plant Growth Regulator (Registration Number 25609), to full registration without consultation.

The conditions for full registration of Retain Technical Powder were the submission of an oncogenicity study in mice and a one-year oral toxicity study in dogs with an emphasis on testicular and spermatogenic endpoints.

The conditions for full registration of Retain Plant Growth Regulator were the submission of a pesticides handler's exposure database assessment, a dermal absorption study, and a dislodgeable foliar residue study.

Chemistry Assessment

Technical product

Common Name: Aviglycine hydrochloride
Chemical Name: (*E*)-L-2-[2-(2-aminoethoxy)vinyl]glycine hydrochloride

Retain Technical Powder has the following properties:

Property	Result
Colour and physical state	Beige to off-white powder
Nominal concentration	86%
Odour	Amine-like odour
Density at 24°C	0.36-0.48 g/mL
Vapour pressure	N/A
pH	6.9±0.4 (1% solution)

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Solubility in water	39.6-47.2 g/100mL
n-Octanol/water partition coefficient (K_{ow})	N/A

The chemistry requirements for Retain Technical Powder have been completed.

End-use product

Retain Plant Growth Regulator is a powder containing the active ingredient aviglycine hydrochloride at a nominal concentration of 15.0%. This product has a density of 0.63-0.93 g/cm^3 and pH of 5.5±0.2 (10% aqueous solution). The chemistry requirements for Retain Plant Growth Regulator been completed.

Health Assessment

Toxicology summary

A detailed review of the toxicological database for aviglycine hydrochloride was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

Aviglycine hydrochloride, 80.6% (90% for inhalation), was considered to be of low acute toxicity by the oral route and of slight toxicity by the inhalation route in Sprague Dawley rats. It was also of low acute toxicity by the dermal route in New Zealand White rabbits. It was slightly irritating when applied to the skin or eyes of New Zealand White rabbits. Results of skin sensitization testing in Hartley guinea pigs, using the Buehler method were inconclusive.

Retain Plant Growth Regulator was of low acute toxicity by the oral route in Sprague Dawley rats and by the dermal route in New Zealand White rabbits. It is slightly toxic to Sprague Dawley rats by the inhalation route. It was minimally irritating when applied into the eyes or to the skin of New Zealand White rabbits. Skin sensitization was not tested for the formulated product as a waiver request was submitted based on the findings of the sensitization study in the technical grade active. Since the sensitization testing in the technical grade active was inconclusive, the waiver request was refused and Retain is considered a dermal sensitizer.

Absorption and excretion of single oral doses of aviglycine hydrochloride was rapid. A range of 56.6-60.4% of the administered dose was absorbed and subsequently excreted in the urine of the low dose group and 69.2-74.0% in high dose animals. Faeces contained 11.4-14.4% of the administered dose for both groups. Expired air yielded about 18.1-22.3% of the administered dose for the low dose group and 5% for the high dose group. Within 7 days, 4.3-4.7% of the administered dose remained in the carcasses of low dose animals and 6.6-8.4% of high dose animals. Tissue residues in general declined rapidly, with the highest levels occurring in the liver, kidney, pancreas, and gastrointestinal tract.

Metabolites were not well characterized. Two metabolites were identified as acetylated parent at either the α or terminal amine groups. A large proportion of excreted radioactivity consisted of polar metabolites which could not be characterized adequately by mass spectrometry. Only 12.5-13.8% of high dose and 3.6-4.1% of low dose parent was excreted unmetabolized in the urine. In faeces, less than 1% aviglycine hydrochloride was excreted unmetabolized. A quantitative sex difference was not observed.

A short-term dermal study showed no significant skin irritation after repeated applications of aviglycine hydrochloride to the shaved skin of albino rats. There was no toxicity associated with treatment.

In subchronic and chronic toxicity studies, aviglycine hydrochloride targeted the following organs: liver, kidney, testes, epididymides, pancreas, thymus, spleen, and eyes. Generalized toxicity was observed in rats, mice and dogs as decreases in body weight, body weight gain, food consumption and/or food efficiency. Liver toxicity was evident in most studies including vacuolation, increased size and weight, and hepatocyte hypertrophy. A subsequent mechanistic study was conducted that supports the hypothesis that aviglycine hydrochloride inhibits the conversion of cystathionine in rats, which in turn may account for some of the aforementioned signs of toxicity. Testicular effects included vacuolation, interstitial cell atrophy, tubular atrophy, decreased weights, and mineralization. Sperm numbers and production were decreased. The number of abnormal sperm was increased. Thymus toxicity included decreased weight, lymphoid depletion, cysts, and atrophy. Testicular, pancreatic and thymus observations were originally considered potentially endocrine mediated; however, a subsequent mechanistic study was conducted to assess androgenic, anti-androgenic, estrogenic and anti-estrogenic activities in HeLa cells which provided no evidence of change in hormone related activity.

A one-year dog study with emphasis on testicular effects was requested by the PMRA. A waiver request was submitted for this study on the basis that the observed effects were not likely endocrine related. Subsequently the request was granted based on a review of all the available data.

Long term studies in rats provided no evidence of treatment-induced oncogenicity. In the mouse study, an increase in hepatocellular adenoma was observed. However, these effects were present at dose levels that exceeded the maximum tolerated dose, therefore, they were not considered relevant for human health assessment.

Aviglycine hydrochloride was negative for genotoxicity in a battery of tests conducted, including: the Ames Bacterial Mutation Test, an in vitro mammalian chromosomal aberration assay, an in vivo mammalian cytogenetics study and a forward mutation assay.

There was no evidence of teratogenicity in the developmental toxicity studies of rats and rabbits. As in the subchronic toxicity studies, general toxicity was observed in the dams, as decreased body weight, body weight gain, food consumption, and defecation.

In the reproductive study, generalized toxicity was observed in parental animals as mortality, decreases in body weight and food consumption, and increases in liver weight. At systemically toxic doses, mating and fertility indices were decreased while the number of gravid females with total litter loss was increased. Sperm numbers, motility, and production rates were reduced. The number of morphologically abnormal sperm was increased. Testes and thymus weights were decreased with corresponding histopathology. Mean live litter size and post-natal survival were decreased in treated pups in both generations. Decreased brain weights correlated with reduced growth in utero.

A special study was generated to determine the immunotoxicity potential of aviglycine hydrochloride. Sprague-Dawley rats were treated in the diet for 28 days; some were sacrificed and the rest were allowed to recover for another 28 days. Treatment-related toxicity was similar to that seen in other repeat-dose studies including decreased thymus weight. Aviglycine hydrochloride was found to have a reversible effect on primary antibody responses. The study as a whole did not fulfill all the requirements of an immunotoxicity study and is considered supplemental.

In assessing the occupational and dietary risks from potential exposure to aviglycine hydrochloride products, the standard uncertainty factor (UF) of 100 has been applied to account for interspecies extrapolation and intraspecies variability.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, extensive data are available for aviglycine hydrochloride, including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to identified concerns relevant to the assessment of risk to infants and children, offspring effects identified in the rat reproductive toxicity study (i.e., increased stillbirths, low birth weight, increased total litter loss, decreased litter size and pup care) occurred at a maternally toxic dose. Although the observed effects in the offspring were considered serious end-points, the concern was tempered by the presence of maternal toxicity. The dosage at which offspring effects are observed is 4.0 mg/kg bw/day. When compared with the NOAEL for risk assessment (0.4 mg/kg bw/day), a 6-fold margin is provided. Thus, the end-point selected provided adequate margins to be protective of the pregnant female, and the PCPA factor has been reduced to 1-fold.

Determination of Acute Reference Dose

A toxicity endpoint attributable to a single dose was not identified. Therefore, the establishment of an acute reference dose was not required.

Determination of Acceptable Daily Intake

The recommended ADI for aviglycine hydrochloride is 0.004 mg/kg bw/day. The developmental study in rabbits was considered the most appropriate study to assess chronic dietary exposure. The NOAEL was 0.4 mg/kg bw/day, based on decreased body weights, body weight gains, and food consumption in adults as well as decreased female fetal weights. The standard uncertainty factor of 100 fold is applied to account for intraspecies and interspecies variability. As discussed in the PCPA Hazard Classification section of this document,the PCPA factor has been reduced to 1 fold. The composite assessment factor (CAF) is 100.

The Acceptable Daily Intake proposed is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{0.4 \text{ mg/kg bw/d}}{100} = 0.004 \text{ mg/kg bw/day}$$

Occupational and residential risk assessment

Occupational exposure is characterized as short-term or intermediate and is predominately by the dermal route. There was a 21-day repeat dose dermal toxicity study available, however, it does not account for the treatment-related histopathological endpoints in the one year rat study or the reproductive endpoints in rats. It is recommended that the rabbit developmental study with a NOAEL of 0.4 mg/kg bw/d be used for short-term exposure scenarios. A target margin of exposure (MOE) of 100 is recommended based on 100X to account for intra-species variation and inter-species extrapolation.

A risk assessment for Retain Plant Growth Regulator was conducted for mixers, loaders and applicators and for workers entering treated fields. The proposed use of Retain Plant Growth Regulator should not result in unacceptable exposure to the active ingredient, aviglycine hydrochloride. No unacceptable risk is expected when workers follow the label directions and wear the personal protective equipment identified on the label.

Food residues exposure assessment

Previously reviewed livestock metabolism data and residue data in/on apples were reassessed in the framework of this petition. As Retain Technical Powder is used to formulate Retain Plant Growth Regulator and there are no changes to the existing use pattern, no changes in the magnitude of the residues in food and feed crops are expected. Therefore, no increase in dietary exposure is anticipated.

Based on the maximum residues observed in apples treated according to label directions, maximum residue limits (MRLs) to cover residues of aviglycine hydrochloride in/on apples and processed commodities will be established as shown in Table 1. Residues of aviglycine hydrochloride in processed commodities not listed in Table 1 are covered under established MRLs for the raw agricultural commodity (RAC).

Table 1 Summary of Field Trial and Processing Data Used to Establish Maximum Residue Limit(s) (MRLs)

Commodity	Application Method/ Total Application Rate	PHI (days)	Residues		Experimental Processing Factor	Currently Established MRL	Recommended MRL
			Min	Max			
Apples	Foliar/ 124 g a.i./ha	28	All <LOQ of 0.075 ppm		0.6X in apple juice	None	0.08 ppm

Following the review of all available data, an MRL of 0.08 ppm for apples is recommended to cover residues of aviglycine hydrochloride. Residues of aviglycine hydrochloride in/on apples do not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

Environmental Assessment

An environmental assessment was not required for this application.

Value Assessment

A value assessment was not required for this application.

Conclusion

The PMRA had conducted an evaluation of the subject application and had found the information sufficient to support conversion to full registration of the technical product, Retain Technical Powder, and the end-use product, Retain Plant Growth Regulator.

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