Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 1.3 Application

Application Number: 2022-0851
Application: Changes to Technical Grade Active Ingredient Product Chemistry - Specifications
Product: Flumioxazin Technical
Registration Number: 29233
Active ingredient (a.i.): Flumioxazin
PMRA Document Number: 3445376

Purpose of Application

The purpose of this application was to revise a toxicological reference value based on a new study for Flumioxazin Technical.

Chemistry, Environmental and Value Assessments

Chemistry, environmental and value assessments were not required for this application.

Health Assessments

Toxicology Summary

There was no evidence of increased sensitivity of the young in the inhalation developmental toxicity study in rats. Parental rats exhibited evidence of toxicity with decreased body weight, body weight gains, increased reticulocyte counts and increased post-implantation loss per dam, increased early resorptions per dam and decreased viable fetuses per dam. At the same dose, there were increases in malformations in the offspring such as ventricular septal defects and tracheal and long bone malformations consistent with effects seen in the oral and dermal developmental toxicity studies in rats. Toxicokinetic investigations in the same study determined that internal exposure in dams is more than 5X higher following inhalation exposure compared to oral exposure. The reduced viability and malformations in rats at maternally toxic doses presented a significant concern, which is accounted for in the risk assessment.

Pest Control Products Act 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 (PCPA) requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the 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[1].

[1] SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

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With respect to the completeness of the toxicity database, extensive data were available on flumioxazin including three developmental toxicity studies in rats (oral, dermal and inhalation), a developmental toxicity study in rabbits, a two-generation reproduction study in rats, and several supplemental developmental mechanistic studies in rats, rabbits, and mice.

With respect to concerns regarding potential prenatal and postnatal toxicity, there is evidence of increased sensitivity of rat fetuses and pups compared to the adult animals via both oral and dermal routes and a serious effect in offspring in the presence of maternal toxicity via the inhalation route. In the oral and dermal rat developmental toxicity studies, decreased pup viability as well as visceral and skeletal malformations were observed at doses with no maternal toxicity. In the inhalation rat developmental toxicity study, the decreased pup viability and the same visceral and skeletal malformations observed in the oral and dermal developmental toxicity studies were observed at a dose that caused decreased body weight and body weight gain and increased reticulocytes in the dams. The two-generation rat reproduction study also showed a decrease in the number of live pups and decreased pup viability in the absence of maternal toxicity. Toxicokinetic studies in pregnant rats showed that flumioxazin crosses the placenta and enters the fetus within two hours of dosing and a very small amount of flumioxazin in the fetus (relative to the total dose given to the dam) is sufficient to cause the observed effects. Both malformations and mortality occurred following a single dose of flumioxazin.

Overall, the database is adequate for determining the sensitivity of the young. There is a high level of concern for sensitivity of the young based on the seriousness of the endpoint (death and malformations) observed in the absence of maternal toxicity by the oral and dermal routes of exposure. Therefore, the full 10-fold PCP factor was retained for scenarios in which the endpoint of neonatal death/malformation was used to establish the point of departure for assessing risk to women of reproductive age. For the inhalation route of exposure, the fetal effects were considered serious endpoints although the concern was tempered by the presence of maternal toxicity. Therefore, the PCPA factor was reduced to 3-fold when using the rat inhalation developmental toxicity study to establish the point of departure for assessing risks to women of child-bearing age.

Occupational Toxicology Reference Values

Dermal

For short- and intermediate-term dermal exposures, the fetal cardiovascular malformations in the dermal rat developmental study at 100 mg/kg bw/day provide the most appropriate endpoint. The NOAEL for this endpoint was 30 mg/kg bw/day. The standard uncertainty factors of 10-fold each have been applied to account for intraspecies variability in toxicological responses and interspecies extrapolation. As the worker population could include pregnant and lactating women, it is necessary to ensure adequate protection of the fetus or the nursing infant who may be exposed via their mother. In light of concerns regarding pre- and post-natal toxicity, a 10-fold uncertainty factor was applied to these endpoints. Therefore, the target MOE is 1000.

Inhalation

For short and intermediate term inhalation exposures, the fetal cardiovascular malformations in the inhalation rat developmental study at 0.020 mg/L provide the most appropriate endpoint. The NOAEL for this endpoint was 0.010 mg/L (equivalent to 2.10 mg/kg bw/day). The standard

uncertainty factors of 10-fold each have been applied to account for intraspecies variability in toxicological responses and interspecies extrapolation. As the worker population could include pregnant and lactating women, it is necessary to ensure adequate protection of the fetus or the nursing infant who may be exposed via their mother. In light of concerns regarding pre- and post-natal toxicity a 3-fold uncertainty factor was applied to these endpoints. Therefore, the target MOE is 300.

Occupational and dietary exposure assessments were not required for this application.

Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided, and has found the information acceptable to revise a toxicological reference value for Flumioxazin Technical.

References

PMRA Document Number	References
3324301	2021, Amendment of Toxicological Endpoints for Flumioxazin EZ Herbicide, DACO: 4.1
3324302	2017, Interpretation of the Results of "A 6-Hour Nose-Only Inhalation Prenatal Developmental Toxicity Study of Flumioxazin in Rats (Study No. Wil-118117)", DACO: 4.1,4.5.2
3324303	2016, An Inhalation Method Development and Validation Study of Flumioxazin for Aerosol Generation and Exposure Atmosphere Characterization, DACO: 4.5.2
3324304	2017, A 6-Hour Nose-Only Inhalation Dose Range-Finding Prenatal Developmental Toxicity Study of Flumioxazin in Rats, DACO: 4.5.2
3324305	2017, A 6-Hour Nose-Only Inhalation Prenatal Developmental Toxicity Study of Flumioxazin in Rats, DACO: 4.5.2