Evaluation Report for Category B, Subcategory 4.6 Application

Application Number: 2008-5941
Application: B.4.6- Fulfill conditions of registration on a product with full registration
Product: Check Mite + Bee Hive Pest Control Strip
Registration Number: 27147
Active ingredients (a.i.): Coumaphos (COU)
PMRA Document Number: 2009320

Purpose of Application

The purpose of this application was to address additional toxicology data requirements triggered by re-evaluation for Check Mite + Bee Hive Pest Control Strip (Reg. No. 27147).

Chemistry Assessment

A chemistry assessment was not required for this application.

Health Assessments

As a result of the recent re-evaluation of coumaphos (PACR2003-04; RRD2004-21), the following confirmatory data were required to support the continued registration of coumaphos and any expansion of coumaphos use:

- a mouse carcinogenicity study should be repeated with adequate dose levels (DACO 4.4.2)
- delayed neurotoxicity studies by the oral and dermal routes that include an assessment of neurotoxic esterase (NTE) activity (DACO 4.5.10)
- a developmental neurotoxicity (DNT) study (DACO 4.5.14)

With the current application, the registrant provided a DNT study with coumaphos, a rationale to waive the requirement for a repeat mouse carcinogenicity study, and studies in hens by the oral and dermal routes that assessed NTE activity. A comparative cholinesterase assay, not available at the time of the re-evaluation, was also considered with the current application. In light of the new data available for coumaphos, dietary reference doses, toxicological endpoints selected for occupational exposure risk assessments, and factors applied in the risk assessment were re-considered.

In the DNT study, the maternal No Observed Adverse Effect Level (NOAEL) was set at 1 ppm (0.22 mg/kg bw/day) based on inhibition of erythrocyte cholinesterase activity on lactation day 21 at the Lowest Observed Adverse Effect Level (LOAEL) of 5 ppm (1.06 mg/kg bw/day). The offspring NOAEL was set at 5 ppm (1.06 mg/kg bw/day) based on inhibition of brain (females only) and erythrocyte cholinesterase activity on lactation day 21 at the LOAEL of 30 ppm (7.4 mg/kg bw/day).

In the comparative cholinesterase assay, a NOAEL of 0.25 mg/kg bw was established in neonatal rats. This NOAEL was based on inhibition of erythrocyte and brain cholinesterase at the LOAEL of 0.5 mg/kg bw. The NOAEL for cholinesterase inhibition in maternal animals was set at 1 mg/kg bw, indicating that the young animal is more sensitive to the cholinesterase inhibiting effects of coumaphos than the adult animal after a single, direct dose.

The applicant did not provide any additional information that would warrant the removal of extra factor applied to the risk assessment, the lack of an adequately conducted mouse carcinogenicity study. Overall, the data available indicated that the mice could have tolerated a higher dose in the carcinogenicity study. Therefore, the additional factor of 3-fold applied to the chronic dietary risk assessment was retained.

The applicant provided studies to demonstrate that coumaphos does not inhibit NTE activity. Overall, the weight of the evidence suggests that coumaphos does not cause delayed neurotoxicity. Therefore, the factor of 3-fold applied previously to the risk assessment is no longer relevant.

Pest Control Products Act (PCPA) Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the PCPA requires the application of an additional 10-fold factor to take into account potential prenatal and postnatal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. 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 pertaining to the exposure of and toxicity to infants and children, the database contains the full complement of required studies including a multigeneration reproduction study in the rat, developmental toxicity studies in the rat and rabbit, and a developmental neurotoxicity study in the rat. A comparative cholinesterase assay in the rat is also available for coumaphos.

With respect to identified concerns relevant to the assessment of risk to infants and children, inhibition of cholinesterase activity was the endpoint of concern identified in the database for coumaphos. The reproduction and DNT studies did not provide any indication of increased susceptibility in the offspring compared to parental animals for this or any other endpoint, nor were any adverse effects observed in the fetus in the developmental toxicity studies. Sensitivity of the young was observed in the comparative cholinesterase study following direct dosing. The endpoint for cholinesterase inhibition in the young was well-characterized in the comparative cholinesterase study and the endpoints used for the risk assessment were selected to ensure

protection of this sensitive sub-population. On the basis of this information, the PCPA factor was reduced to 1-fold.

Dietary Reference Doses

In light of the new information available for coumaphos, the Acute Reference Dose (ARfD) has been revised from 0.002 mg/kg bw to 0.0025 mg/kg bw. This is based on the NOAEL of 0.25 mg/kg bw in neonates in the comparative cholinesterase assay, and a Composite Assessment Factor (CAF) of 100 to account for interspecies extrapolation and intraspecies variability. As indicated above, no additional factor for delayed neurotoxicity was required and the PCPA factor has been reduced to 1-fold.

The maternal NOAEL in the DNT study was lower than the NOAEL selected previously in the re-evaluation for establishment of the Acceptable Daily Intake (ADI). With the removal of the factor of 3-fold to account for delayed neurotoxicity, the ADI was revised from 0.0003 mg/kg bw/day to 0.0007 mg/kg bw/day, based on the maternal NOAEL of 0.22 mg/kg bw/day in the DNT study, and a CAF of 300. The maternal NOAEL in the DNT study was based on erythrocyte cholinesterase inhibition. The CAF includes the standard uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variability , as well as an uncertainty factor for the database deficiency of 3-fold to account for the lack of an adequately conducted mouse carcinogenicity study.

Toxicological Endpoints for Occupational Risk Assessment

The new information provided with this application did not impact the toxicological endpoints selected for the dermal and inhalation risk assessments. For short-term dermal exposure (1-7 days), the 5-day dermal toxicity study in female rats with a NOAEL of 5 mg/kg bw/day was selected. This NOAEL was based on inhibition of brain cholinesterase activity at the LOAEL of 10 mg/kg bw/day. For intermediate-term dermal exposure (8-30 days), the 21-day dermal toxicity study in rats with a NOAEL of 0.5 mg/kg bw/day was selected. This NOAEL was based on inhibition of erythrocyte cholinesterase activity at the LOAEL of 1.1 mg/kg bw/day. There were no inhalation studies available for coumaphos; therefore an oral toxicity study was selected for short- to intermediate-term inhalation exposure. The 13-week oral study in rats with a NOAEL of 0.2 mg/kg bw/day was selected. This NOAEL was based on inhibition of erythrocyte cholinesterase at the LOAEL of 0.5 mg/kg bw/day.

With the removal of the factor of 3-fold to account for delayed neurotoxicity, the target Margin of Exposure (MOE) for short- to intermediate-term dermal and inhalation exposure risk assessments changed from 300 selected previously to 100. This target MOE was considered adequate to protect the worker population, which may include pregnant women, since studies in which the young were indirectly exposed to coumaphos (i.e, studies including the reproduction study, the developmental toxicity studies and the DNT study in which the young were exposed *in utero* or potentially through lactation) did not demonstrate sensitivity of the young. Therefore, there was no residual concern with respect to the offspring of female workers through indirect exposure.

A health risk assessment was conducted for Check Mite + Bee Hives Pest Control Strip product. The proposed product use pattern is within the currently registered use pattern for coumaphos. Therefore, it is not expected that the health risk to handlers and by-standers will increase over currently registered products containing coumaphos for the same use. A food exposure assessment was not required for this application.

Environmental and Value Assessment

Environmental and value assessments were not required for this application.

Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided in support for the product, Check Mite + Bee Hive Pest Control Strip, and has found the toxicology data sufficient for the additional requirements.

References

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