Health Canada Santé Canada

Section 12 Notice **Additional Information Required to Fulfill the Terms and Conditions for Conditional Registration**

Product Name: ***Pyrimethanil Technical Fungicide***
Registration Number: ***28010***
Application Number: ***2007-1408***
PMRA # ***1579872***

During the conditional registration period which has been granted to December 31, 2010, the following information is to be generated and must be provided to the Pest Management Regulatory Agency **by September 1st, 2010** and should indicate the DACO numbers specified. A partial response to the outlined Terms and Conditions will not be accepted.

Part 4 TOXICOLOGY

DACO: **4.1**
Title: **Summary - Toxicology Profile**
Details: The PMRA assessment of 2-amino-4,6-dimethylpyrimidine (AN7) concluted that it is of moderate acute oral toxicity in rats (♂,♀ LD_{50} = 735 mg/kg bw; C.I 575-939 mg/kg bw), however, the study conclusions were limited by the early culling of animals with apparent clinical toxicity within the first day of dosing. The majority of animals were not assessed for the 14-day observation period and therefore, a better estimation of the LD_{50} was not possible. Although the surviving animals recovered from clinical signs by the end of the study period in the absence of body weight effects or gross pathological findings, it is not possible to conclude whether the actual LD_{50} of AN7 is higher, based on the uncertainty surrounding the survival outcomes of the moribund animals. No further acute toxicity or sub-chronic studies were submitted for AN7, and the acute and short-term toxicological effects were not well characterized (e.g., establishment of NOAEL; comparison of treatment-related effects between AN7 and pyrimethanil). In addition, a severe endpoint (sacrificed moribund) occurred in animals treated with 800-1600 mg/kg bw AN7 (less than the OECD recommended limit dose of 2000 mg/kg bw) that was not observed in the acute toxicity studies with pyrimethanil at significantly higher dose levels (>4000 mg/kg bw).

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A limited number of toxicology studies were submitted for the characterization of 2-amino-4,6-dimethylpyrimidine. Limitations in the acute oral study precluded an accurate estimation of the LD_{50} in rats and therefore, AN7 is considered to be of moderate toxicity via the oral route. AN7 was not mutagenic in the bacterial reverse mutation assay; however, no further genotoxicity studies were submitted. The SAR data submitted for structurally similar compounds were reviewed as additional information using a weight-of-evidence approach. Structural alerts for carcinogenicity were noted for AN7, however, these "flags" should not raise any additional concerns based on the molecule's structural similarity to the parent and the large margin between the reference doses for pyrimethanil and key toxicological endpoints in the database provided that AN7 is not more toxic than pyrimethanil.

Based on the uncertainty surrounding the acute oral study, the increased sensitivity of rats compared to mice in the short-term studies for pyrimethanil, and the uncertainty of the toxicological effects of AN7 after acute and short-term exposure, **a short-term (90-day) oral study in rats is required**. Future submission of these data will not preclude the request of additional toxicology data for ANT7 and is dependent on the outcome of full evaluation.