Registration Decision RD2019-13

Bixafen and F9651-2 Fungicide

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Registration Decision Statement[1] for Bixafen and F9651-2 Fungicide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting registration for the sale and use of F9650 Technical Fungicide, containing the technical grade active ingredient bixafen, and F9651-2 Fungicide, containing the technical grade active ingredients bixafen and tebuconazole, to control foliar diseases on wheat, barley, oats and soybean.

This decision is consistent with the Proposed Registration Decision PRD2019-04, *Bixafen and F9651-2 Fungicide*, which contains a detailed evaluation of the information submitted in support of this registration. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable. See Appendix I for a summary of comments received during the consultation process as well as Health Canada's response to these comments.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2019-04) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).

Any person may file a notice of objection[2] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[1] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

[2] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1. Comment regarding the subchronic toxicity study in the mouse

The registrant enquired why a NOAEL (no observed adverse effect level) was not established for the 28-day toxicity (dietary) study on C57BL/6J mice (PMRA# 2642774), specifying that they think the NOEL/NOAEL should be 100 ppm (17 and 21 mg/kg/day in males and females, respectively).

Response from the PMRA:
This subchronic toxicity study in the mouse is a range-finding study and does not satisfy the guideline requirement (OECD 407) for a repeat-dose oral study in mice. The PMRA does not establish NOAELs for non-guideline and/or range-finding studies.

2. Comment regarding the subchronic toxicity study in the rat

The registrant enquired why a NOAEL was not established for the 28-day toxicity (dietary) study on Wistar rats (PMRA# 2642773), specifying that they think the NOEL/NOAEL should be 350/50 ppm (25 or 4.1 mg/kg/day in males and females, respectively).

Response from the PMRA:
This subchronic toxicity study in the rat is a range-finding study and does not satisfy the guideline requirement (OECD 407) for a repeat-dose oral study in rats. The PMRA does not establish NOAELs for non-guideline and/or range-finding studies.

3. Comment regarding the coagulation parameters

As stated in the Proposed Registration Decision PRD2019-04, *Bixafen and F9651-2 Fungicide,* in the absence of a known mechanism of action for bixafen on coagulation, the PMRA concluded that any significant effect on coagulation parameters was treatment-related and adverse.

In turn, the registrant submitted a position paper and commented: “Toxicity data available on bixafen through guideline studies and additional mechanistic studies do not indicate any adverse effect of bixafen on blood coagulating parameters. A hemorrhagic syndrome was produced in male rats and to a lesser extent, in male mice in subacute and subchronic exposure studies with bixafen. Initially this was thought to be an intrinsic toxicological property of the compound, though no common structural basis with warfarin or other known anti-coagulant rodenticides could be established. It was evident that the anticoagulant property only pertained to studies in rodents and was only seen in males. It was then discovered, that this finding was due to a complete lack of vitamin K in these batches of diet. Apart from the fact that male rats naturally require about 25% more vitamin K than female rats it was also discovered that CYP450 2B and/or CYP450 3A4 isoenzyme inducers could also exacerbate clotting problems and Bouwman *et al.* hypothesized that such inducers could result in a reduction in one or more coagulation factors activated by the vitamin K cycle when vitamin K is absent.[3] Furthermore, two mechanistic studies were run to investigate the effect of vitamin K deficiency in the diet and the hemorrhagic syndrome. These mechanistic studies demonstrate unequivocally that bixafen exerts

[3] *Toxicology*, 75 (1992):109-120.

an effect on male rats in the presence of dietary deficiency of vitamin K, resulting in prolongation of PT and APTT and hemorrhage. In addition, a review of the literature[1] indicates that inducers of CYP450 2B enzymes can cause this effect in male rats, and this is believed to be the mechanism for the coagulation effects seen with bixafen. Once the dietary level of vitamin K was restored, there was no further anti-coagulation effect of bixafen on male rats. These data show that the accidental deficiency of vitamin K in the rodent diet has contributed to the high rate of mortality and hemorrhagic syndrome observed in the chronic toxicity studies with bixafen. The addition of vitamin K in the diet allowed the conduct of chronic studies and established the toxicity profile of bixafen as well as clear NOAELs. Thus, there are no adverse effects on coagulating parameters among animals when treated with bixafen."

Response from the PMRA:
Although some evidence to the contrary exists in the published scientific literature, the PMRA cannot rule out an effect of bixafen on blood coagulation. The 90-day oral toxicity study in the rat (PMRA# 2756732) showed that after a 90-day dietary treatment with bixafen, coagulation parameters were affected, but returned to control values after a 28-day recovery period despite the fact that the diet was depleted in vitamin K during the recovery period. On this basis, the PMRA concluded that bixafen may have an effect on coagulation parameters that may have been exacerbated by a vitamin K deficiency in the diet.

4. Comment regarding maximum residue limits (MRLs) for milk, meat and meat byproducts

The registrant commented that the exclusion of sorghum from the dietary burden resulted in the difference between the milk tolerances between the United States and Canada, and that this could result in a trade irritant, therefore encouraging the PMRA to harmonize the tolerance with that of the United States Environmental Protection Agency. The registrant further stated: "An MRL of 0.2 ppm may be considered suitable only if relevant to the dietary burden of beef cattle and disregarding dairy cattle. Combining fat, meat and meat byproducts could result in a trade irritant between the United States and Canada. Compared to meat byproducts, meat is the major exporting commodity and meat byproducts would be considered the secondary market. [FMC Corporation] would encourage PMRA to split the meat and meat byproduct MRLs as done by [the United States Environmental Protection Agency] to avoid future trade issues."

Response from the PMRA:
The PMRA understands the registrant's stance regarding the alignment of Canadian MRLs and American tolerances for bixafen in/on edible livestock commodities so as not to create potential trade irritants. However, the PMRA has considered these points and concluded that the American sorghum residue trial data will remain excluded from the dietary burden calculations and that the proposed Canadian MRLs will not be revised.

In response to the specific comment concerning the exclusion of sorghum data from the dietary burden calculation, it is noted that a use on sorghum is being requested in the United States only and not for registration in Canada. According to standard practice, only residue values for the feedstuff items for which the active ingredient has a registered or proposed use in Canada should be included in the dietary burden calculation.

The rationale for not including imported feed commodities in the dietary burden calculator is that fluctuations in Canadian production due to weather can have a significant impact on the supplies of the field crops used as livestock feed, which may need to be supplemented by imported animal feed byproducts. However, there must be an economic advantage to use imported feed byproducts or nonconventional feeds, given that the location of the farm relative to the source of feed byproducts will have a major influence on feed byproduct costs. While it is recognized that some farmers can get feed byproducts from crops that are not grown in Canada (such as cottonseed meal), this does not constitute a constant and widespread practice for economic reasons. Moreover, some feed byproducts may be available in a limited geographic area due to transportation costs or concerns with shelf-life of the feed byproducts.

Furthermore, MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the crop field trials used to generate residue chemistry data. For livestock commodities, differences in MRLs can also be due to different livestock feed items and practices. As such, the proposed Canadian MRLs to cover residues of bixafen and the metabolite bixafen-desmethyl in/on milk, meat and meat byproducts are not being revised at this time.