Re-evaluation Note REV2016-12

Special Review Decision: Fluazinam

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Special Review Decision

Pursuant to subsection 17(2) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) initiated a special review of all registered pest control products containing fluazinam, as a result of the 2010 Norwegian decision to prohibit all uses of fluazinam in Norway (Rotterdam Convention, 2010). The PMRA evaluated the aspects of concern that prompted the special review in accordance with the subsection 18(4) of the *Pest Control Products Act*. The aspects of concern relevant to the environment were identified as: persistence and potential carryover in soil, potential for long-range atmospheric transport, potential bioaccumulation, and risk to earthworms. In addition, potential developmental and reproductive effects related to human health were also considered in this review. The proposed special review decision was published for consultation in the Re-evaluation Note REV2015-08, *Special Review of Fluazinam: Proposed Decision for Consultation* (Canada, 2015) and it outlines the Agency's proposed decision and the reasons for it. Appendix I summarizes the comments received during the consultation period and provides the PMRA's response to these comments.

Comments received during the consultation process were taken into consideration in making this special review decision, and they did not result in changes to the proposed regulatory decision as described in REV2015-08. Therefore, the PMRA, under the authority of the *Pest Control Products Act*, is confirming the current registration of pest control products containing fluazinam in Canada.

Please refer to the Regulatory Directive DIR2014-01, *Approach to Special Reviews*, for details of the PMRA's special review approach.

Other Information

Any person may file a notice of objection[1] regarding this decision on fluazinam within 60 days from the date of publication of this special review decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website, Request a Reconsideration of Decision, or contact the PMRA's Pest Management Information Service.

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

Appendix I Comments and Responses

The PMRA received comments from stakeholders in response to Re-evaluation Note REV2015-08, *Special Review of Fluazinam: Proposed Decision for Consultation* (Canada, 2015). The PMRA consolidated and summarized the comments related to this special review and provides responses below.

1.0 Science Evaluation

1.1 Comment on persistence and potential carryover in soil

The Rotterdam Convention Prior Informed Consent (PIC) Circular XXXII (2010) explaining Norway's decision to ban fluazinam states persistence as an underlying reason for the ban. In REV2015-08, the PMRA states that fluazinam is persistent in aerobic soil conditions and has the potential for carryover into the next growing season. The PMRA provides no justification for the proposed decision to accept this environmental hazard (which Norway has deemed unacceptable), other than to note that the hazard is stated on the product label, along with a recommendation to not apply the product if it was used in the previous season. The PMRA does not provide any evidence that the recommended best practice is being followed and is effectively mitigating the environmental hazard. No information is given about the usage profile of the end-use product Allegro in Canada or environmental monitoring to test for accumulation of fluazinam in Canadian soils.

PMRA Response

The PMRA follows a risk-based scientific approach in determining the potential risks to the environment from the use of pesticides. The persistence of fluazinam was considered for assessing potential risks to non-target organisms taking into consideration the rate, number and frequency of applications and the environmental fate properties such as persistence in the environment.

Fluazinam is a fungicide currently registered for use as a foliar application by ground or aerial equipment (Allegro 500F Agricultural Fungicide, registration number 27517). Best practices to minimize accumulation in soil are currently included on the product label. The product is recommended for use as part of an Integrated Pest Management program, which includes resistance management recommendations to delay fungicide resistance. Examples of these recommendations include: not applying more than three consecutive sprays before switching to a fungicide with a different mode of action; only applying the product based on an integrated disease management program (such as scouting, historical information related to pesticide use and crop rotation); and discontinuing use if disease continues to progress after treatment.

The PMRA routinely conducts active prevention and monitoring programs across the regulated community and follows up on situations of reported or suspected pesticides misuse, working in partnership with our federal and provincial colleagues.

1.2 Comment on risk to earthworms

Another underlying reason for the Norwegian ban, according to the PIC Circular XXXII (2010), was that "fluazinam is extremely reproductively toxic to earthworms and the risk of effects on earthworms is very high." The PMRA evaluation of acute risks to earthworms does not address the concerns about reproductive toxicity. With respect to chronic effects, REV2015-08 mentions only that the PMRA considered the results of one field study reported by Norway that indicated no statistically significant reduction in total biomass or population size. There is no discussion of the evidence that led Norway to conclude that fluazinam is extremely toxic to reproduction for earthworms, or of why the PMRA and the Norwegian Food Safety Authority have come to opposite conclusions regarding the chronic toxicity of fluazinam to earthworms.

Furthermore, in the assessment of acute risks to earthworms, it is not clear whether the PMRA has taken into account fluazinam's persistence in soil and potential to accumulate in soils. REV2015-08 states that the estimated environmental concentration is calculated based on the maximum registered application rates, but multiple applications (in the same growing season, or subsequent growing seasons) could result in greater exposure.

PMRA Response

Norway assessed acute and chronic (reproductive) risks assuming the predicted initial environmental concentration in soil of 0.99 mg/kg soil based on eight applications at a rate of 200 g a.i./ha[2] and DT_{50} of 226 days (Norway, 2009). Based on this, acute risk to earthworms was not of concern. Chronic risk to earthworm was identified; however, it was reported that "there have been field studies carried out that do not show any effects at relevant dosages" (Norway, 2009). Overall, the 2010 Norwegian decision reported that, "The model calculations showed a transgression of the threshold value for chronic toxicity (reproduction effects) for earthworms, with a factor of 25. Field studies were carried out over one year, but the Expert Group feels that these studies do not necessarily weaken the indications from the laboratory experiments. The Expert Group deems that the risk of effects on earthworms is very great" (Norway, 2010).

The PMRA conducted a Canadian relevant risk assessment based on the Canadian use pattern. As indicated above in response to Comment 1.1, the persistence of fluazinam was considered for the exposure estimation. The PMRA estimated an environmental concentration in soil of 2.2 mg a.i./kg soil based on conservative assumptions, including the maximum cumulative application rate of 5.3 kg a.i./ha/year (based on six applications at 875 g a.i./ha at 7-day spray intervals), a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, bare soil application, and the most conservative soil half-life value of 200 days. Based on this, acute risks to earthworms were not of concern (risk quotient < 0.004). Based on the NOEC < 0.175 mg a.i./kg soil (Norway, 2009), the chronic (reproduction effects) risk quotient was 12; and therefore, exceeded the level of concern of 1. However, results from a one-year field study with five species of earthworms did not show a statistically significant reduction in total biomass or population size (Norway, 2009). Although a potential chronic risk was identified based on an estimated concentration in soil (using conservative assumptions), the available field study did not identify a significant chronic effect of fluazinam on the earthworm population. Further, as noted in REV2015-08, the PMRA

[2] a.i. = active ingredient

concludes that bioaccumulation of fluazinam is not expected to be of concern. Based on the above, the PMRA concludes that fluazinam is unlikely to have a potential chronic (reproductive) effect on the earthworm population. This is consistent with the European Commission's conclusion, which indicated that, "Whereas the reproductive study on earthworms did not meet the Annex VI trigger, a field study with earthworms addressed the long term risk to earthworms" (European Food Safety Authority, 2008).

1.3 Comment on human health effects (developmental and reproductive)

The PIC Circular XXXII (2010) explaining Norway's decision to ban fluazinam also states that fluazinam is "classified with possible risk of harm to the unborn child." The PMRA agrees that developmental studies indicate increased sensitivity of the fetus and applies a threefold margin of safety in calculating the allowable level of human exposure, pursuant to the *Pest Control Products Act.* Section 19(b)(iii) of the *Pest Control Products Act* generally requires a 10-fold margin of safety to take into account potential prenatal toxicity "unless, on the basis of reliable scientific data, the Minister has determined that a different margin of safety would be appropriate." REV2015-08 provides no rationale for maintaining only a threefold margin of safety. In light of the Norwegian decision to ban fluazinam, citing risks to the fetus, a higher margin of safety should be considered. As REV2015-08 does not specify the exposure levels (doses) calculated for various scenarios, it is not clear whether applying higher margin of safety would change the outcome of the risk assessment.

PMRA Response

As indicated in the comments, when assessing risks from potential exposure from 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 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, unless a different margin of safety is determined to be appropriate on the basis of reliable scientific data.

The PMRA evaluated the toxicity database for fluazinam (Canada, 2003; Canada, 2008a; Canada, 2008b), and found that the database contains the full complement of required studies including developmental studies in rats and rabbits, a reproductive toxicity study in rats, and a developmental neurotoxicity study in rats. No evidence of neurotoxicity was observed and there was no residual uncertainty relating to the completeness of data with respect to infants and children. Based on the available information, in addition to the standard uncertainty factors (10-fold for interspecies extrapolation and 10-fold for intraspecies variability), the 10-fold factor was reduced to threefold, to protect for potential sensitivity of the young (Canada, 2008a; Canada, 2008b). This Composite Assessment Factor of 300-fold provides a 1900-fold margin of safety to the no observed adverse effects level (NOAEL) for developmental effects in the rabbit developmental study, thus providing a large protective margin. As such, the PMRA concludes that a reconsideration of the reduction of the *Pest Control Products Act* factor to threefold for fluazinam is not warranted and the outcome of the human health risk assessment remains unchanged.

1.4 Comment on selection of the acute reference dose

REV2015-08 does not explain the PMRA's decision to base the Acute Reference Dose (ARfD) for the general population on the NOAEL of 4 mg/kg bw/day, rather than the lower intermediate-term dermal and inhalation NOAEL of 1.9 mg/kg bw/day that was identified for liver pathology. Has the PMRA conducted a risk assessment, including potential developmental effects, based on this alternative endpoint?

PMRA Response

The ARfD is the dose to which an individual could be exposed on a single occasion and expect no adverse health effects. In accordance with the Science Policy Note, SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment* (Canada, 2008c), the ARfD is based on the most relevant endpoint from the database and divided by a multiple of factors. The selection of the most appropriate study, endpoint and NOAEL for risk assessment takes into consideration which human subpopulations may be exposed, the route of exposure and the anticipated duration and frequency of exposure.

As indicated in REV2015-08, the PMRA established an ARfD of 0.013 mg/kg bw for the general population based on the most relevant endpoint, a maternal NOAEL of 4 mg/kg bw/day from the rabbit developmental study (lowest observed adverse effect level, LOAEL = 7 mg/kg bw/day based on decreased food consumption, which was noted within the first few days of dosing). As indicated in Proposed Registration Decision PRD2008-08, *Fluazinam*, the ARfD incorporates an uncertainty factor of 100-fold to account for intraspecies and interspecies variability, and an additional threefold margin of safety to protect for sensitivity of the young. The ARfD takes into consideration the potential developmental and reproductive effects of fluazinam. The intermediate-term dermal and inhalation endpoint based on the NOAEL of 1.9 mg/kg bw/day from the rat two-generation reproduction study (used to assess occupational scenarios) was not considered the appropriate endpoint for establishing the ARfD, as the effects noted required multiple exposures over a longer period of time, and, therefore, are not relevant to ARfD setting (Canada, 2008a; Canada, 2008b).

1.5 Comment on chronic effects

The PMRA appears to have overlooked chronic effects in its evaluation of human health effects for the special review of fluazinam. The SAgE Pesticides database maintained by the Quebec Ministry of Agriculture, Fisheries and Food (Ministre de l'Agriculture, des Pêcheries et de l'Alimentation du Québec) classifies fluazinam as very highly toxic in terms of long-term effects on mammals, and has effects on the endocrine system. The latter, in particular, may be relevant to the evaluation of developmental toxicity.

PMRA Response

As indicated in REV2015-08, the toxicity database for fluazinam was considered complete (Canada, 2003; Canada, 2008a; Canada, 2008b) and included subchronic and chronic toxicity studies, as well as developmental and reproductive toxicity of fluazinam, all of which were evaluated by the PMRA (Canada, 2003; Canada, 2008a) (response to comment 1.3). As

discussed in these documents, in establishing the Acceptable Daily Intake for assessing chronic risk, standard uncertainty factors were applied to account for intraspecies and interspecies variability and the 10-fold factor required by the *Pest Control Products Act* was reduced to threefold to account for the endocrine-related toxicity noted in the database. The exposure and risk assessments for registered end-use products containing fluazinam indicated that risks to human health are not of concern when used according to the label directions.

1.6 Comment on cumulative effects of the pest control products

Section 19(2)(b)(i) of the *Pest Control Products Act* requires consideration of "cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity." There is no indication that the PMRA has considered cumulative effects in this special review evaluation of potential developmental and reproductive effects.

PMRA Response

The PMRA considers cumulative health effects of pest control products when a common mechanism of toxicity is identified with other pest control products. Health Canada's Science Policy Notice SPN2001-01, *Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment* (Canada, 2001) describes the steps for identifying mechanisms of toxicity of pesticides that cause a common toxic effect, the types of data needed and their sources, how these data are to be used in reaching conclusions regarding commonality of mechanisms of toxicity, and the criteria Health Canada applies for categorizing pesticides for the purpose of cumulative risk assessments. A common mechanism of toxicity has not been identified for fluazinam in relation to other pest control products, nor is this active ingredient considered to produce a metabolite common to other active ingredients (United States, 2015). Therefore, a cumulative risk assessment is not required for fluazinam.

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