Registration Decision RD2023-02

Fenazaquin, Magister SC Miticide/Fungicide, and Magus SC Miticide

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Publications
Pest Management Regulatory Agency
Health Canada
2 Constellation Drive
8th floor, A.L. 2608 A
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
pmra.publications-arla@hc-sc.gc.ca

Information Service:
1-800-267-6315
pmra.info-arla@hc-sc.gc.ca

Canada

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Under the authority of the *Pest Control Products Act* (PCPA), pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as comments if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the section of Evaluation Approach of this document.

Registration Decision Statement[2] for Fenazaquin

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 Fenazaquin Technical Miticide/Fungicide, Magister SC Miticide/Fungicide and Magus SC Miticide containing the technical grade active ingredient fenazaquin to control certain mites, psylla, whitefly, and powdery mildew on a variety of crops and ornamental plants.

The Proposed Registration Decision PRD2022-11, *Fenazaquin, Magister SC Miticide/Fungicide, and Magus SC Miticide*, containing the detailed evaluation of the information submitted in support of this registration, underwent a 45 day consultation period ending on October 13, 2022. 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. Health Canada received comments (and information) relating to the health, environmental and value assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

Comments and responses

Comments on the occupational exposure assessment

Comments on the feasibility of the proposed restricted-entry intervals (REIs): Comments on the feasibility of the proposed REIs from the public and growers groups were sought by Health Canada in PRD2022-11: "*Health Canada is seeking comments from stakeholders on the agronomic feasibility of the 10-day restricted-entry interval (REI) for hand harvesting stone fruits, 17-day REI for hand thinning pome and stone fruits, and the 22- and 15-day REI for girdling and training grapes, respectively, in addition to any other proposed REIs*."

In response, comments from the Ontario Fruit & Vegetable Growers' Association (OFVGA) were received concerning the agronomic feasibility of the proposed REIs for grapes, pome fruit and stone fruit crops. The communication states: "After consultation with our members, the **OFVGA does consider the proposed REIs presented in PRD2022-11 for grapes, pome fruit, and stone fruit to be agronomically feasible within our current practices**. The addition of

[1] Information Note – Determining Study Acceptability for use in Pesticide Risk Assessments

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

fenazaquin miticide will bring value to our sector to control mite pests. While we do consider the proposed REIs to be agronomically feasible, the proposed REIs for pome fruit and stone fruit are substantially longer than other registered miticide products in these crops. Any flexibility in the proposed REIs notably for hand thinning in pome and stone fruit would provide additional utility for our members when using fenazaquin."

Health Canada response

Based on the occupational exposure risk assessment, in order to protect postapplication workers from unacceptable exposure levels, the proposed REIs of hand thinning activities in pome and stone fruits cannot be revised to a shorter interval. Taking into account OFVGA's consideration that the proposed REIs for grapes, stone fruits and pome fruits are feasible, from an occupational exposure perspective, these uses and associated postapplication activities can be supported, as proposed in PRD2022-11.

Ecojustice submitted the following comments on behalf of Ecojustice, Friends of the Earth, Justice for Migrant Workers collective, Environmental Defence, Safe Food Matters, the David Suzuki Foundation and Prevent Cancer Now on the registration of pest controls products containing the active ingredient fenazaquin.

Comments related to the proposed mitigation measures: Ecojustice is seeking clarification on the occupational exposure assessment and is questioning whether the proposed mitigation measures are realistic: whether wearing the required PPE for greenhouse ornamental workers is realistic given greenhouses are a hot environment, whether the REIs of 15 and 22 days for grapes are agronomically feasible, and why greenhouse uses are approved if the REIs were not agronomically feasible.

Health Canada response

Health Canada registers pesticide uses for which feasible mitigation measures can be determined, as required by risk assessments. PRD2022-11 specifies that the required REIs for **greenhouse vegetables** (41 days for harvesting and all other activities), **indoor/greenhouse ornamentals grown for cut flowers** (10 days for hand harvesting, disbudding, hand pruning) **and outdoor ornamentals grown for cut flowers** (9 days for hand harvesting, disbudding, hand pruning) were not considered agronomically feasible; therefore, these uses are not supported (pg. 4 and Table 11 - Postapplication Dermal Exposure and Risk Estimates for Fenazaquin).

The REIs for other listed uses are acceptable and are found on page 7–8 of PRD2022-11. As noted in the previous comment, stakeholder input was sought in PRD2022-11 on the agronomic feasibility of the proposed REIs of 10 days for hand harvesting stone fruits, 17 days for hand thinning pome and stone fruits, and 22 and 15 days for girdling and training grapes, respectively. Please refer to the previous comment from OFVGA confirming feasibility of these REIs after consulting with their members.

The personal protective equipment (PPE) required to reduce potential exposure of workers to fenazaquin is listed on pg. 4 and 6 of PRD2022-11. Coveralls are required for many pesticide products used in greenhouses. Health Canada's PMRA has consulted with registrants, industry

associations, and pesticide user groups and has also visited many different greenhouses. During these consultations, the appropriate use of PPE has been discussed. Greenhouse growers rely on pesticides as important tools and have indicated they will follow the labels and take responsibility for the safety of their employees. The PMRA will not implement label changes that are neither feasible nor safe. However, in the case of worksite hazards, such as higher temperatures, the greenhouse supervisor, under the applicable provincial *Occupational Health and Safety Act*, is responsible for identifying work hazards and resolving safety concerns. They can do this by scheduling application during cooler times of the day, implementing many breaks, having cold water available, and creating shorter shifts where workers can take turns wearing the appropriate PPE. Alternatively, they can choose to use a different product or spray equipment that does not require the same level of PPE.

For the two fenazaquin end use products, the required PPE was selected for two reasons. First, the acute toxicology of the end use products indicated that they are moderately irritating to the skin and, consequently, they were designated as a skin irritant, which requires coveralls during use. Second, the risk assessment results were considered, which take into account the short term-toxicology reference values of the active ingredient with the amount of expected exposure. Hence, the use of PPE that meets the standard for protection of human health under the *Pest Control Products Act* were proposed.

Comments on the toxicology assessment

Comment related to the PCPA Factor as it pertains to the rabbit developmental toxicity study: Ecojustice stated that the full PCPA factor should have been applied in the risk assessment given the lack of an "acceptable developmental neurotoxicity study in the rabbit", and that the explanation provided in PRD2022-11 justifying the application of the reduced PCPA factor of threefold was inadequate and lacked transparency.

Health Canada response

Although the comment makes reference to a developmental neurotoxicity study in the rabbit, it is the prenatal developmental toxicity study in the rabbit that is discussed in detail in PRD2022-11. For clarification, prenatal developmental toxicity studies follow OECD Test Guideline 414, and are typically conducted in both rats and rabbits to support a pesticide registration. In these studies, the test material is administered to pregnant animals during gestation with the purpose of identifying potential effects on fetal development. A developmental neurotoxicity (DNT) study follows a different protocol, which is outlined in OECD Test Guideline 426. DNT studies are typically conducted in rats, and involve dosing of maternal animals during gestation and lactation, with subsequent testing of the offspring at various times during their post-natal development and into adulthood for neurobehavioural and neuropathological effects.

As described in PRD2022-11, some limitations in the available rabbit prenatal developmental toxicity study conducted with fenazaquin were identified during the review of the toxicology database. These limitations included a high number of maternal deaths caused by technical errors and several abortions that occurred after the cessation of dosing which resulted in an insufficient number of litters available from the high-dose group for an adequate assessment of potential

developmental toxicity. Furthermore, the lack of treatment-related effects in this study called into question the adequacy of the dose levels selected. While this study on its own was not considered acceptable for regulatory purposes, the study provided useful information to use in a weight of evidence assessment, which took into consideration limitations in the study and results from the rest of the fenazaquin database, to conclude that additional factors were not warranted in this situation. This weight of evidence assessment is explained in further detail below.

As noted in the *Pest Control Products Act* hazard characterization section of PRD2022-11, completeness of the data with respect to exposure of and toxicity to infants and children is a consideration in the determination of the magnitude of the PCPA factor. However, there is overlap between the use of an uncertainty factor to account for database deficiencies and a PCPA factor to account for the completeness of the data with respect to the toxicity to infants and children. Accordingly, as outlined in Science Policy Note SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*, it is Health Canada's practice to address most uncertainties relating to the completeness of data with respect to the toxicity to infants and children (or for any subpopulation) through the application of an appropriate uncertainty factor for database deficiency. Therefore, as part of the review of the fenazaquin toxicology database, consideration was given to the acceptability of the rabbit developmental toxicity study in the context of the overall uncertainty in the hazard characterization.

As indicated in PRD2022-11, it was concluded that an additional uncertainty factor to account for the limitations in the rabbit developmental toxicity study was not warranted. When considering the dose levels tested in this study in relation to the points of departure established in other studies in the database as well as those selected for human health risk assessment (discussed further below), there is a low level of concern for potential developmental toxicity that may have been observed at the high-dose level in the rabbit, had a sufficient number of litters been available for evaluation.

The dose levels used in the rabbit developmental toxicity study were 0, 3, 13, and 60 mg/kg bw/day. No issues were identified with the adequacy of the dose groups of 0, 3, or 13 mg/kg bw/day, in that there was a sufficient number of litters to adequately assess developmental toxicity at these dose levels. No treatment-related effects on the developing fetus were observed when pregnant rabbits were dosed with 3 or 13 mg/kg bw/day. The point of departure selected for assessing risks to human health was determined to be the NOAEL of 5 mg/kg bw/day from the 2-generation reproductive toxicity study, and the total magnitude of the uncertainty factors and the PCPA factor resulted in a composite assessment factor of 300. Accordingly, the amount of fenazaquin that can be ingested orally without any human health concerns for both a single day (acute or ARfD) and over a lifetime (chronic or ADI) was determined to be 0.02 mg/kg bw/day. This acceptable human exposure level is 650-fold lower than the dose level of 13 mg/kg bw/day in the rabbit developmental toxicity study, at which an acceptable number of litters was available for assessment and there were no developmental effects observed. As such, in this case, it was determined that an adequate margin of safety exists between acceptable levels of human exposure for fenazaquin and a dose level administered to pregnant rabbits that did not result in any concern for developmental toxicity, thus negating the need for any additional uncertainty factors relating to the limitations in the rabbit developmental toxicity study.

Of note is that the European Food Safety Authority (EFSA) review of 2013, cited by Ecojustice in their comments related to other aspects of the fenazaquin review, did not identify any concerns with respect to the acceptability of the rabbit developmental toxicity study. The United States Environmental Protection Agency (USEPA) identified similar concerns as the PMRA but also concluded that a new rabbit developmental toxicity study was not needed, as the dietary reference doses established by the USEPA are well below the high dose level of 60 mg/kg bw/day in the rabbit developmental toxicity study, and the rat was more sensitive to fenazaquin than the rabbit in the developmental toxicity studies.

With respect to the adequacy and transparency of Health Canada's explanation justifying the reduction of the PCPA factor to threefold, the summary provided under section 3.1.2 of PRD2022-11 discusses Health Canada's rationale for determining the magnitude of the PCPA factor that was applied for the assessment of fenazaquin. It describes the various considerations that went into the decision by Health Canada scientists to reduce the PCPA factor to threefold, including consideration of the completeness of the database and potential concerns relating to pre- and post-natal toxicity. Overall, it was concluded that the database was adequate for assessing sensitivity of the young and that there was a low level of concern for sensitivity of the young, as effects in the young were well-characterized and occurred in the presence of maternal toxicity. Although a serious endpoint (pup mortality) was observed at the LOAEL in the 2-generation reproductive toxicity study, concern for this finding was tempered by the fact that it was observed in the presence of parental toxicity. Based on this information, the PCPA factor was reduced to threefold. Reduction of the PCPA factor to threefold in this situation is consistent with the guidance outlined in SPN2008-01, which discusses the considerations that go into the determination of the PCPA factor.

Comments related to the neurotoxic potential of fenazaquin: Several comments from Ecojustice related to the potential for fenazaquin to elicit neurotoxicity. Ecojustice noted that several endpoints observed in the toxicology database for fenazaquin were considered as evidence of generalized toxicity in PRD2022-11, but could be suggestive of possible neurotoxicity, and that evidence of neuropathology had also been noted by the USEPA. Ecojustice also noted that PRD2022-11 did not indicate whether a subchronic neurotoxicity study was required or provided for the evaluation of fenazaquin.

Health Canada response

The toxicology database for fenazaquin included an acute oral neurotoxicity study in rats and a subchronic (90-day) dietary neurotoxicity study in rats. The subchronic neurotoxicity study was provided to Health Canada upon request during the review of the fenazaquin database, in order to ensure sufficient data to evaluate the potential for neurotoxic effects in animals. Both the acute and subchronic neurotoxicity study are summarized in PRD2022-11.

Health Canada concluded that there was no evidence of **selective** neurotoxicity in the database for fenazaquin. The clinical signs of toxicity identified by the commenter, such as decreased motor activity, sluggish arousal, abnormal respiration, unusual posture, spastic gait, ataxia and excess salivation, urine-stained abdominal fur, and loss of righting reflex, occurred at the same or higher dose levels than those that also caused generalized systemic toxicity and in

some cases significant body weight loss and mortality. This suggested that the effects were attributable to generalized toxicity, rather than evidence of selective neurotoxicity. Therefore, Health Canada concluded that there is an overall low level of concern for neurotoxicity within the fenazaquin database.

The neuropathology identified in some USEPA documentation relates to an earlier conclusion by the USEPA regarding a finding of mild neuronal vacuolization in the dorsal root ganglia, skeletal muscle fiber degeneration, and nerve fiber degeneration in the thoracic spinal cord at the highest dose level tested in the acute oral neurotoxicity study in rats. The Health Canada review of the acute neurotoxicity study with fenazaquin took into consideration various USEPA documents, and included a detailed assessment of these findings.

The USEPA's consideration of these findings is summarized in its human health risk assessment document of August, 2014, for proposed new uses on almonds and cherries (PMRA# 2962619). In that document, the USEPA outlined their reasons for eventually concluding that the neuropathological findings initially reported in the acute neurotoxicity study were **not related** to treatment. Health Canada agreed with the USEPA's final conclusion, based on the fact that the incidences of the neuropathological findings in high-dose animals were similar to or less than those in control animals when the incidences of both sexes were combined.

Based on the absence of treatment-related neuropathological findings in either the acute or subchronic neurotoxicity study, combined with the absence of neurobehavioural findings suggestive of selective neurotoxicity, there was an overall low level of concern for neurotoxicity within the fenazaquin database. As such no additional neurotoxicity studies were required.

Comments related to the acute reference dose: Ecojustice questioned Health Canada's reliance on the point of departure of 5 mg/kg bw/day from the rabbit developmental toxicity study for the establishment of the acute reference dose, given the limitations in that study. Ecojustice also noted that the acute reference dose is "at the NOAEL for 90-day oral and chronic toxicity in dogs", citing a 2007 Pesticide Fact Sheet for fenazaquin issued by the USEPA.

They also noted that the European acute reference dose is set at 0.1 mg/kg bw based on effects seen in dams in the rat developmental toxicity study, and called upon Health Canada to explain why a "less precautionary approach" to the acute reference dose was taken when compared to the European Union.

Health Canada response

The ARfD of 0.02 mg/kg bw established by Health Canada is actually more conservative (that is, more precautionary), by a factor of five, than the European ARfD of 0.1 mg/kg bw established in 2013 by EFSA, which was based on a maternal NOAEL of 10 mg/kg bw/day from the rat developmental toxicity study and a safety factor of 100.

As outlined in PRD2022-11, Health Canada established an acute reference dose (ARfD) of 0.02 mg/kg bw of fenazaquin. This was based on the offspring NOAEL of 5 mg/kg bw/day from the 2-generation oral reproductive toxicity study in rats, not the point of departure in the rabbit developmental toxicity study as incorrectly reported by Ecojustice. As indicated above for the

ADI, the ARfD is also 650-fold lower than the dose level of 13 mg/kg bw/day in the rabbit developmental toxicity study for which an acceptable number of litters was available for assessment and there were no developmental effects observed.

Health Canada also established NOAELs of 5 mg/kg bw/day in the 90-day and 1-year oral toxicity studies in dogs. However, the offspring NOAEL of 5 mg/kg bw/day from the 2-generation reproductive toxicity study in rats was selected for establishment of the ARfD since the endpoint of pup mortality at the LOAEL is considered to be relevant to an acute exposure scenario, and in order to provide sufficient protection against the endpoint of concern of pup mortality through the application of the PCPA factor. The effects at the LOAEL in the other studies are not considered to result from a single (acute) exposure.

Comments related to the reproductive toxicity studies: Ecojustice commented that the increased pup mortality observed in the reproductive toxicity studies was "dismissed" in PRD2022-11, and that "additional uncertainty factors" were reduced on the grounds that the effects occurred in the presence of parental toxicity. Ecojustice called on Health Canada to explain why pup mortality is not of concern, as the presence of parental toxicity does not "provide assurance that there is reasonable certainty that no reproductive harm will occur".

Health Canada response

In PRD2022-11, Health Canada states that the pup mortality observed in the 2-generation reproductive toxicity study with fenazaquin is considered to be a serious endpoint. Thus, Health Canada did not dismiss this finding or indicate that the endpoint was not of concern. Due to the seriousness of this finding, it was determined to be the critical endpoint on which human health reference values were based, and the PCPA factor was retained. However, considering that toxicity to the parental animals was observed at the same dose level as the pup mortality, the PCPA factor was reduced to threefold. The lines of evidence that Health Canada applies when evaluating the degree of concern for prenatal and postnatal toxicity are outlined in Table 1 of SPN2008-01, and include, among other factors, both seriousness of the endpoint and sensitivity of the young. In the case of fenazaquin, concern for the seriousness of the endpoint in the young was tempered by the presence of parental toxicity at the same dose level, thus resulting in a reduction in the PCPA factor to threefold, consistent with the guidance outlined in SPN2008-01.

Comments related to the adrenocortical adenomas in female hamsters: Ecojustice commented that Health Canada merely stated in PRD2022-11 that the increased incidence of adrenocortical adenomas in female hamsters was considered equivocal based on the weight of evidence "without further explanation" and that there was no explanation as to why this study was given little weight. They further commented that it was not clear what other studies Health Canada relied on "to establish that fenazaquin is not carcinogenic or why".

Health Canada response

As outlined in PRD2022-11, Health Canada evaluated the carcinogenic potential of fenazaquin based on a review of long-term studies in rats and hamsters. Health Canada concluded that there was no evidence of tumourigenicity in the 2-year dietary combined chronic toxicity/oncogenicity

study in rats, and there was equivocal evidence of tumourigenicity in the 18-month gavage oncogenicity study in the hamster. In the hamster, increased incidences of adrenocortical adenomas in females at the mid- and high-dose levels were deemed to have an equivocal relationship to treatment based on several considerations, which are summarized in PRD2022-11. For example, there was significantly greater survival at study termination at the mid- and high-dose levels where the adenomas were observed, indicating that the increased tumour incidences could have been due to the older age of the majority of the animals at termination when compared to the control. Historical control data suggested that the background incidence of adrenocortical adenomas in females sacrificed at 19–24 months increases by 2.7-fold compared to those necropsied at 13–18 months, demonstrating that the incidence of adrenocortical adenomas increases significantly later in life. Furthermore, the incidence of adrenocortical adenomas at the mid-dose level in the fenazaquin study fell within the range of historical control incidences, and the incidence in high-dose females was slightly higher than the upper end of the historical range. Therefore, based on the available information, the evidence for tumourigenicity in this study was considered to be equivocal. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of fenazaquin. That is, the ADI provides a margin of 750-fold to the dose level at which an equivocal increase in adrenocortical adenomas was observed in female hamsters.

Comment related to the methods used to assess carcinogenicity: Ecojustice stated that Health Canada lacks coherent guidelines on how to assess carcinogenicity, and asked for confirmation as to the process Health Canada uses to assess the carcinogenicity of pesticides, and whether Health Canada uses the USEPA cancer guidelines.

Health Canada response

Health Canada's approach to assessing the carcinogenicity of pesticides is described in the guidance document *A Framework for Risk Assessment and Risk Management of Pest Control Products*. In summary, the cancer assessment for pesticides is based on evidence from cancer studies in at least two species together with evidence from in vitro and in vivo genotoxicity studies. These studies are typically carried out at dose levels that are much higher than expected human exposures. In many cases these are also complemented with studies that shed light on the mechanism or biological mode of action by which the pesticide causes cancer. The outcome of the animal studies together with mechanistic considerations are used in a weight-of-evidence approach to decide if a pesticide is likely to pose a cancer hazard to humans. If a potential cancer hazard is identified, a cancer risk assessment is conducted to ensure that exposure to the pesticide will not result in unacceptable risk to humans. This type of approach is consistent with that used by other international agencies. Although the general cancer risk assessment approach used by the USEPA is consistent with that of Health Canada, the USEPA also employs a classification system and applies a descriptor, such "carcinogenic to humans" or "suggestive evidence of carcinogenic potential", based on several lines of evidence, which then determines how the USEPA will regulate the pesticide. The lines of evidence used by the USEPA are also taken into consideration by Health Canada in assessing cancer hazard.

In summary, Health Canada's approach is to identify whether a pesticide has the potential to pose a cancer hazard based on the weight of evidence (consideration of several lines of evidence), and to ensure adequate protection against that hazard regardless of tumour type, species, or sex of the animal affected through the cancer risk assessment.

Comment related to the genotoxic potential: Ecojustice stated that there is evidence that fenazaquin is mutagenic in vitro, inducing mutations, chromosome aberrations, and polyploidy, citing a conclusion by EFSA in 2013, and states that this genotoxic potential is not addressed in PRD2022-11.

Health Canada response

A summary of all of the available genotoxicity, including mutagenicity, studies with fenazaquin is included in PRD2022-11. Several studies were available for review. Clearly negative results were obtained in a bacterial reverse mutation assay, an in vitro forward mutation assay in mammalian cells, an in vitro and an in vivo unscheduled DNA synthesis assay, and two in vivo micronucleus assays.

Two in vitro chromosomal aberration assays in Chinese hamster ovary cells were available. An equivocal result was obtained in one study, in which a non-concentration-related increase in chromosomal aberrations in the presence of metabolic activation was observed at only one harvest time-point. The second in vitro chromosomal aberration assay in Chinese hamster ovary cells demonstrated a clear negative result. Overall, Health Canada concluded that the weight of evidence, which included negative effects in multiple in vivo studies, indicated that fenazaquin was negative for potential genotoxicity and mutagenicity. Of note is that EFSA also concluded in their 2013 assessment that overall, fenazaquin is considered unlikely to be genotoxic in vivo.

Comment related to the mechanism of toxicity: Ecojustice commented that Health Canada's conclusion that a common mechanism of toxicity has not been identified for fenazaquin and other pesticides requires further explanation. They stated that it is unclear why the "suggested" common mechanism of cellular toxicity with other pesticides in vitro does not result in a cumulative assessment for fenazaquin.

Health Canada response

There is some evidence from the literature that a similar response was observed when neuronal cells were exposed in vitro to fenazaquin and other pesticides that share the same mode of action in insects. However, the in vitro test systems used in these literature studies do not mimic real-world exposure of whole organisms, such as laboratory animals or humans, to these compounds. These in vitro test systems do not account for toxicokinetic processes, such as how the pesticide may be absorbed and distributed in the whole body, or metabolized or detoxified by the liver. Therefore, when determining if a cumulative assessment was warranted for fenazaquin, Health Canada placed more weight on the results from the available in vivo animal toxicology studies conducted with fenazaquin and related pesticides, which do account for these toxicokinetic processes, rather than on in vitro test results. The toxic effects that were observed in the available mammalian in vivo studies conducted with fenazaquin were considered to be related to general

toxicity, and could not be linked to the results from the in vitro studies. Consistent with Health Canada's approach to the cumulative assessment of pesticides, as outlined in Science Policy Note SPN2018-02, *Cumulative Health Risk Assessment Framework*, generalized or non-specific toxic effects that have many possible unrelated causes are not appropriate to form the basis of grouping pesticides with a common mechanism of toxicity. Therefore, it was determined that a cumulative assessment for fenazaquin was not required.

Comment related to repeat-exposure inhalation toxicity: Ecojustice indicated that the waiver granted for the repeat-exposure inhalation toxicity study is not sufficiently justified, and that no scientific basis is provided for the use of endpoints from oral toxicity studies in the inhalation risk assessment. They also noted concern for a volatile transformation product of fenazaquin, 4-tert-butylstyrene, and the absence of a phototransformation study in air. Ecojustice also stated that Health Canada does not indicate in PRD2022-11 whether a subchronic inhalation study was provided.

Health Canada response

As outlined in PRD2022-11, the applicant's request to waive the short-term inhalation toxicity study, which can also be referred to as a subchronic inhalation toxicity study, was found to be acceptable by Health Canada based on several factors, including the low volatility of fenazaquin, the fact that it is difficult to generate particle sizes in the respirable range with fenazaquin, and because margins of exposure were acceptable for the inhalation exposure scenarios when oral endpoints were used in the risk assessment.

As indicated in Table 21 of PRD2022-11, the volatile transformation product of fenazaquin, 4-tert-butylstyrene, was detected in laboratory transformation studies, but is expected to be present at very low levels in the environment. As such, a phototransformation study in air was not required.

Comment related to the toxicity of plant metabolites: Ecojustice commented that, according to European regulators, the plant metabolite TBPE is of higher toxicity than fenazaquin and has a European classification of "possible risk of impaired fertility", "danger of serious damage to health by prolonged exposure if swallowed", and "risk of serious damage to eyes". They stated that PRD2022-11 does not acknowledge these characteristics, and noted that Europe established specific reference doses for this metabolite at levels far lower than the dietary reference doses established for fenazaquin by Health Canada.

Health Canada response

The results from the mammalian studies with TBPE that were available to Health Canada for review indicated that it was of **lower** toxicity than fenazaquin when administered via the oral route as a single dose or daily for 28 days. The European review of fenazaquin cited the same data for TBPE that were available to Health Canada.

The conclusion by Health Canada took into consideration the fact that toxic effects were observed in repeat-dose oral toxicity studies in rats dosed with TBPE at a higher dose level (approximately 150 mg/kg bw/day) than when compared to fenazaquin (approximately 30 mg/kg bw/day). Of note is that these same effect levels for TBPE and fenazaquin were identified in the European review.

The basis for the European classification of "possible risk of impaired fertility" and "danger of serious damage to health by prolonged exposure if swallowed" is not apparent in their review document, nor is it clear how this classification led to the European conclusion that TBPE is of higher toxicity than fenazaquin. However, it is important to note that the regulation of chemicals in Europe is based largely on a hazard-based approach, which results in difficulty drawing conclusions about risk as it does not take into consideration potency or exposure.

Given that a full toxicology database was not available for TBPE, there was insufficient information for Health Canada to fully characterize the overall toxicity of TBPE relative to fenazaquin. Therefore, to be protective, TBPE was included in the residue definition for assessing risks from exposure via drinking water, since it was identified as a major transformation product of fenazaquin in the environment. A separate human health reference value for TBPE was not established by Health Canada as the available information did not indicate that TBPE was of higher toxicity than fenazaquin, and thus Health Canada considered the ADI and ARfD established for fenazaquin to be protective of potential toxicity of TBPE.

Comments on supported and unsupported uses

Comments related to clarification of supported and unsupported uses: Ecojustice is seeking clarification on which uses are proposed for registration, indicating that "PRD2022-11 states that greenhouse uses are not supported from a dietary risk perspective" and "other parts of PRD2022-11 confirm that greenhouse uses for vegetables, cut flowers and ornamentals are not supported on the basis of occupational risks". They state that, with respect to dietary risks, what the PMRA assessed and what it concluded from the assessment was not explained.

Health Canada response

As detailed in PRD2022-11 (page 164–166, Table 34 – List of Supported Uses), the uses proposed for registration are on bushberries, caneberries, cucurbit vegetables, fruiting vegetables, low growing berries, pome fruits, small fruit vine climbing (except fuzzy kiwifruit), stone fruits, ornamental plants (including fruit and nut tree seedlings, non-bearing fruit and nut trees), indoor ornamental plants and plantscapes, and established outdoor ornamental landscape plantings. It is specified that **indoor uses are for ornamentals only** (greenhouse ornamentals, including fruit and nut tree seedlings, and indoor plants and plantscapes). Uses on greenhouse vegetables and on cut flowers (indoor/greenhouse or outdoor) are not supported, and do not appear in Table 34.

PRD2022-11 specifies that the use on greenhouse vegetables is not supported from a dietary risk perspective since the greenhouse trials submitted for cucumbers, peppers and tomatoes are not considered acceptable, as they are not representative of the Canadian use pattern and the crops were not grown under conditions typical of greenhouses in Canada. As such, only outdoor uses

on cucurbit vegetables and fruiting vegetables are proposed for registration, as listed in Table 34. The PMRA's assessment of the nature and magnitude of residue studies and the conclusions of the assessment are detailed in Tables 16 (Residue Analysis), 17 (Integrated Food Residue Chemistry Summary) and 18 (Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment) on pg. 80-103 of PRD2022-11.

PRD2022-11 also specifies that the REIs for **greenhouse vegetables**, and for **indoor/greenhouse and outdoor ornamental cut flowers** were not considered agronomically feasible; therefore, these uses are not supported. Other uses listed in Table 34, including cucurbit and fruiting vegetables grown in the field, and indoor or outdoor ornamental plants (except those grown for cut flowers) are acceptable from mixer/loader/applicator, postapplication worker and residential exposure perspectives, and are proposed for registration. The analyses are detailed in Tables 7–15 on page 64–74 of PRD2022-11.

Comments on the environmental risk assessment

Comment: Ecojustice stated that "The proposed registration decision indicates that fenazaquin is soluble in water and slightly to moderately persistent in aquatic systems where it accumulates in sediments. It is clear from the proposed registration decision that a number of scenarios including runoff and spray drift create exposures of concern for a variety of aquatic organisms. Fenazaquin is highly toxic to aquatic organisms. In the runoff scenario risk quotients were exceeded by a significant margin for nearly all aquatic species. We do not understand the commentary in the proposed decision that suggests that exposures are reduced by the lack of suspension in the water column. Aquatic organisms depend on sediments and are exposed to sediments when feeding. The decision lacks transparency about how the PMRA considered or did not consider exposure of aquatic organisms through sediments."

Health Canada response

The EFSA review cited in the comment was used in part to inform the PMRA's review of aquatic toxicity studies for fenazaquin. Similar to the EFSA review, the PMRA found that fenazaquin was highly toxic to some aquatic organisms. The calculation of risk quotients (RQs) integrates both toxicity and exposure information, including the toxicity endpoints that indicate high toxicity. As noted in the comment, the RQs for most aquatic organisms in both the spray drift and runoff scenarios exceeded the level of concern (LOC; 1 for aquatic organisms).

A spray buffer zone is the downwind distance between the point of direct pesticide application and the nearest downwind boundary of a given sensitive habitat. Spray buffer zones are determined using standard spray drift deposition models for different types of application equipment. Parameters considered in the models include application rate and pattern, chemical half-lives in the environment, and toxicity to non-target organisms. Mandatory aquatic spray buffer zones of 2 to 55 m for fenazaquin end-use products mitigate risk to aquatic organisms from spray drift exposure to an acceptable level (in other words, RQs are less than the LOC).

Runoff RQs reflect pelagic exposure since they are based on estimated environmental concentrations in the water column and the most conservative set of toxicity endpoints corresponding to water-only exposure tests (except the water-spiked sediment and water test with *Chironomus riparius*, a sediment-dweller). The RQ values over 10 include chronic risk to *Daphnia magna* (RQ: 24.5), acute risk to amphibians (RQ: 19.2, based on a surrogate acute freshwater fish endpoint), acute risk to freshwater fish (RQ: 13.8) and acute risk to marine algae (RQ: 12.9). Risks to pelagic freshwater and marine organisms are acceptable given the following considerations:

- laboratory aquatic biotransformation studies and a higher-tier microcosm study demonstrate that fenazaquin concentrations are unlikely to be sustained in the water column due to the rapid transfer of fenazaquin out of the water phase, thereby reducing exposure;
- the lack of treatment-related effects on *D. magna* and bluegill sunfish exposed to fenazaquin in a microcosm study at a maximum nominal concentration that falls within the range of EECs used in the RQ calculations;
- the high likelihood of quick and effective dilution of marine inputs by water currents, which is not accounted for in the model used to generate EECs in the runoff scenario;
- conservativisms in the calculation of EECs including: 1) use of maximum application rates, 2) use of the longer of two available aqueous photolysis half-lives and aerobic aquatic half-lives, 3) assumption of stability in sediment, 4) assuming runoff input from application on an adjacent field for 50 consecutive years, and 5) the final selection of EECs from the upper range of modelled EECs; and
- the lack of aquatic incident reports in the United States (as of last available update in 2015), where fenazaquin has been registered since 2010 for use on agricultural crops and ornamentals.

The runoff scenario RQs for *C. riparius,* a sensitive sediment-dweller that is an important aquatic prey species, were also calculated considering sediment pore water concentrations. An RQ of 22.9 was calculated using a modelled EEC in pore water (0.0048 mg a.i./L) and a NOAEC (0.00021 mg a.i./L) in pore water. A 7% reduction in rate of emergence compared to the control group was observed at the LOAEC (0.0009 mg a.i./L in pore water, RQ of 5.3). The risks to benthic organisms are acceptable considering the low level of effect observed at the LOAEC and the conservatisms in the calculation of EECs mentioned above for the water column, which are also applicable to pore water EECs.

A hazard statement warning users of toxicity of fenazaquin to aquatic organisms and precautionary statements to reduce runoff and contamination of water bodies are required on the product label.

Comment: Ecojustice commented that the proposed decision is incredibly vague about the potential impacts on pollinators. The proposed decision states that exposure to pollinators can occur from direct contact with spray or spray drift, contact with sprayed surfaces, or from ingestion of contaminated food. Ecojustice states that numerous comments in the proposed decision indicate that fenazaquin poses potential unacceptable risks including to endangered pollinator species.

Health Canada response

PRD2022-11 indicates that the screening level risk assessment, uncertainties with the available semi-field studies, and risks to other non-Apis bees pointed to a need to mitigate risks to pollinators through label statements. When used according to the instructions on the product label, risks to pollinators are acceptable.

Comment: Ecojustice commented that the proposed decision fails to establish reasonable certainty that no harm will occur to pollinators simply because label statements provide language cautioning against application to blooms. The information submitted on risks to bees was stated to be insufficient.

Health Canada response

Submitted information was sufficient to conduct the pollinator risk assessment. The PMRA conducted a pollinator risk assessment using acute and chronic laboratory studies for adult and larval bees, as well as results from foliage residue studies, and semi-field studies. PRD2022-11 explains the uncertainties with the submitted semi-field studies (including that the application rates in semi-field studies were lower than maximum proposed Canadian application rates, and length of time for observation of brood was too short). These uncertainties resulted in conservative pollinator mitigation on the label (in other words, no application during bloom for bee attractive crops). The proposed label statement for outdoor use is not a “cautionary” statement; it is an enforceable limitation on the timing of application. By not allowing application during bloom (for bee attractive crops), exposure of bees to contaminated pollen and/or nectar (bee food source) is limited because there will not be any fenazaquin sprayed on open flowers, in other words, the risk is acceptable.

As well, fenazaquin is not systemic, meaning that any application **before** bloom will not result in residues of fenazaquin in pollen and/or nectar (bee food source), and therefore, this application timing also results in acceptable risk.

Comment: Ecojustice stated that the use of these label statements is not evidence-based as the PMRA has no evidence to support compliance with these label statements on existing products, nor that if followed they would be effective in protecting pollinators from fenazaquin.

Health Canada response

The pesticide label is a legal document, defined under the *Pest Control Products Act*. It is illegal to use a pesticide in any way other than for the purpose and in the manner stated on the label. Health Canada's Pesticides Compliance Program has compliance officers across Canada working to achieve compliance with the *Pest Control Products Act* and Pest Control Products Regulations. Activities regulated under the *Pest Control Products Act* include pesticide manufacturing, transportation, importation, distribution, possession, handling, storage, and use. Compliance officers prioritize and deliver compliance and enforcement activities, as well as develop compliance guidance documents, strategies, and procedures. The ISO 17025 accredited laboratory in Ottawa provides analytical services for detecting and reporting on pesticide misuse. Pesticides are also analysed to determine whether they meet the specifications upon which

registration was granted. For additional information on compliance promotion, monitoring and enforcement as well as annual reports on activities see the Pesticides compliance and enforcement page on Canada.ca. **There have not been compliance issues specific to pollinator protection on any existing registered products according to the summary of the annual reports from 2017 to 2022.**

Comments on effects of mixtures

Comment: Ecojustice commented that Section 8(l) of the Pest Control Products Regulations requires that Health Canada assess the effects of mixtures. The proposed registration decision does not contain this information and the PMRA cannot have reasonable certainty that no harm will occur to human health or the environment without this information.

Health Canada response

Value and efficacy: Section 8(l) of the Pest Control Products Regulations requires that the PMRA assess "the effect of mixing the pest control product or using it simultaneously with other pest control products". Assessment of risks to human health and the environment take into account the proposed conditions of registration. The end-use products containing fenazaquin were not proposed to be mixed or used simultaneously with other pest control products and there are no provisions for any such uses on the product labels.

Toxicology: Section 8(l) of the Pest Control Products Regulations requires that the applicant provide the Minister with any other information that the Minister may require to evaluate the health and environmental risks, including, if relevant to the product and its conditions of registration, the results of scientific investigations respecting the effect of mixing the pest control product or using it simultaneously with other pest control products.

Note that neither of the end-use products associated with the proposed registration of fenazaquin, Magister SC Miticide/Fungicide or Magus SC Miticide, are proposed to be mixed or used simultaneously with other pest control products.

Health Canada assessment of the potential health risks of Magister SC Miticide/Fungicide and Magus SC Miticide included the review of toxicology studies that assessed the acute hazard of the formulated products. These studies define the hazard statements that must appear on the product label specific to each formulated product. Individual formulated products were also used for other studies, such as in the generation of residue chemistry data, or field trials, considered during the risk assessment phase.

Dietary exposure: In terms of dietary exposure, a non-ionic surfactant was included in the spray mixtures for the crop field trials, as indicated in PRD2022-11. As such, the impact of inclusion of a non-ionic surfactant on the magnitude of fenazaquin residues in/on treated crop commodities has been taken into account.

As part of the health and environmental risk assessment, as well as the value assessment, the conditions of use are determined for each formulated product. These conditions of use include, but are not limited to, the rate of application (for example, in grams or kg active ingredient/hectare), the number of applications permitted, the types of application equipment that can be used, the specific uses (for example, specific agricultural crops, or non-agricultural uses), when and how the product is to be used, and the personal protective equipment required. All of these conditions are based on ensuring that the level of human and environmental exposures from the pesticide residues in each formulated product is at, or below, the reference values that are set to protect both human health, and the environment.

Comment on batch data

Comment: Ecojustice commented that "The PRD does not disclose the full list of contaminants that might be present in fenazaquin, and these should be disclosed and consulted upon. The PRD indicates that the end-use products, Magister SC Miticide/Fungicide and Magus Miticide contain the preservative 1,2-benzisothiazolin-3-one which contains "low levels" of dioxins and furans. The PMRA should disclose the specific levels of dioxins and furans. It is clear from the PRD that commercial scale batch data was not provided to establish that dioxins and furans are not present. The PMRA has not explained how it can determine that levels of dioxins and furans in the final end use products are reasonably certain to cause no harm to human health. The PMRA appears to be conditionally registering this product without commercial scale batch data. It is unclear what mechanism the PMRA proposes to use to enforce this additional requirement. The PRD does not explain on what timeline batch data will be provided and whether Canadians and their environment will be exposed to the product without knowing whether it contains serious contamination in the interim. This is particularly concerning given the PMRA's recent lack of attention to the severe contamination of batches of linuron with extremely toxic substances – which it also dealt with after a registration decision. Repeated decisions to defer consideration of batch contamination undermine the PMRAs commitment to eliminate conditional registrations. The product should not be registered until commercially relevant batch data is submitted and the PMRA can determine that it is reasonably certain that no harm to the environment or human health will result from batch contamination. The proposed decision does not indicate what actions PMRA will take if the batch data provided raises human health concerns from contamination or how the public will know when the batch data is submitted, or on what timeline the registrant will be allowed to provide batch data. This approach is non-compliant with section 6(g) of the *Pest Control Products Regulations*."

Health Canada response

As substances subject to Canada's federal Toxic Substances Management Policy (TSMP), the presence and levels of polychlorinated dibenzodioxins and dibenzofurans (PCDDs and PCDFs) are not considered confidential business information. They are not generally published but can be disclosed upon request. Impurities other than those identified in the published List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern are considered confidential business information (CBI) as they can reveal aspects of the manufacturing process.

Dioxins and furans are not expected in technical grade fenazaquin. Very low levels of these impurities are present in the end-use product due to the use of 1,2-benzisothiazolin-3-one as a preservative. Commercial-scale batch data for these impurities in the preservative have been provided for assessment and the very low levels do not pose a concern.

With respect to the requirement for commercial-scale batch data for the fenazaquin technical grade active ingredient, this does not constitute conditional registration. As per the PMRA's Memorandum to Registrants Use of Pilot-Scale Data to Register Multiple Sites for New Active Ingredients, under the specified conditions, product registration can be supported by pilot-scale batch data (including impurities of concern) that are representative of the manufacturing process that will be used for commercial production. All requirements specified in the *Pest Control Products Regulations* section 6(g) are satisfied since complete characterization of all products is provided and evaluated before registration, including any impurities of concern. Therefore, these data are sufficient for the purpose of registration, upon which the registrant is issued a public Section 12 notice outlining the post-market requirement for full-scale batch data as soon as it is available following initiation of commercial production. The timeline specified to submit the commercial scale batch data is not to exceed four years, taking into account that registrants may not begin commercial production immediately at all sites.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2022-11, *Fenazaquin, Magister SC Miticide/Fungicide, and Magus SC Miticide*) are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection[3] 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 and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

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

Evaluation approach

Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if conditions of registration can be established to prevent unacceptable risk impact to human health and the environment.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[4]

Risk and value assessment framework

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[5] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks.[6]

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[7]

Assessments estimate potential health risks to defined populations[8] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of

4 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

5 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*

6 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000

7 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*

8 Consideration of Sex and Gender in Pesticide Risk Assessment

the pesticide in occupational or residential settings, food and drinking water exposure, or exposure when interacting with treated pets. Also considered are the anticipated durations (short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide’s efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

Risk management

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*. Implementation of post-market decisions follow the framework articulated in the Policy on Cancellations and Amendments Following Re-evaluation and Special Review.[9]

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.

[9] PMRA Regulatory Directive DIR2018-01 *Policy on Cancellations and Amendments Following Re-evaluation and Special Review*

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
bw	body weight
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
ISO	International Organization for Standardization
kg	kilogram(s)
L	litres
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
m	metres
mg	milligram(s)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
OFVGA	Ontario Fruit & Vegetable Growers' Association
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
PRD	Proposed Registration Decision
REI	restricted-entry interval
RQ	risk quotient
SPN	Science Policy Note
TBPE	2-(4-tert-butylphenyl) ethanol
USEPA	United States Environmental Protection Agency

References

Published information

PMRA document number	Reference
2962619	2014, Fenazaquin: Human Health Risk Assessment for Proposed New Uses on Almonds and Cherries., DACO: 12.5,12.5.4,12.5.5