Proposed Registration Decision PRD2015-03

Sedaxane

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Overview

Proposed Registration Decision for Sedaxane

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sedaxane Technical, Vibrance 500FS Seed Treatment (containing the technical grade active ingredient sedaxane) and Vibrance XL Seed Treatment (containing the technical grade active ingredients sedaxane, difenconazole and metalaxyl-m) to be used on various crops to control or suppress soil and seed-borne diseases of seedlings and mature plants.

Sedaxane Technical (Registration Number 30435), Vibrance 500FS Seed Treatment (Registration Number 30438; previously known as Sedaxane 500FS Fungicide) and Vibrance XL Seed Treatment (Registration Number 30437; previously known as A16874F) are conditionally registered in Canada. The detailed review of sedaxane can be found in Evaluation Report ERC2012-01, *Sedaxane*. Subsequent to the original applications, the uses on the label of Vibrance 500FS Seed Treatment were expanded to include dried shelled peas and beans (except soybean - Crop Subgroup 6C), corn and the complete Crop Subgroup 20A (rapeseed). The data requirements identified for the conditional registrations are being addressed in the current applications. The current applications were submitted to convert Sedaxane Technical, Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment from conditional registration to full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Sedaxane Technical, Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on sedaxane, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on sedaxane, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of ERC2012-01, *Sedaxane*.

What Is Sedaxane?

Sedaxane is the active ingredient present in the seed treatment products: Vibrance 500FS Seed Treatment (containing sedaxane) and Vibrance XL Seed Treatment (containing sedaxane, difenoconazole, metalaxyl-m). Sedaxane is a fungicide with systemic properties, and it inhibits the normal respiration process in target pathogenic fungi. The sedaxane-based products are used on seed from various crops to control or suppress soil and seed-borne diseases of seedlings and mature plants.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "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."

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

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

Health Considerations

Can Approved Uses of Sedaxane Affect Human Health?

Products containing sedaxane are unlikely to affect your health when used according to label directions.

Potential exposure to sedaxane may occur through the diet (food and water), when handling and applying the product or when entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the active ingredient sedaxane and its associated end-use products, Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment, were of low acute toxicity by the oral, dermal and inhalation routes of exposure. They were minimally irritating to the eyes and non-irritating to the skin, and did not cause allergic skin reactions. Consequently, no hazard signal words are required on the labels.

Health effects in animals given repeated doses of the active ingredient sedaxane included effects on the liver, thyroid and circulatory system. Sedaxane did not cause birth defects in animals. When sedaxane was given to pregnant or nursing animals, effects on the developing fetus (a slight increase in abortions) and juvenile animal (decreased spleen weight) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to sedaxane than the adult animal. Sedaxane caused functional effects, possibly related to the nervous system, at high doses in rats. There was no evidence that sedaxane damaged genetic material but it did, however, cause liver tumours in mice and liver, thyroid and uterine tumours in rats. A cancer risk assessment was conducted based on the uterine tumours found in rats as this was protective of the other tumour types.

The risk assessment protects against the effects of sedaxane by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

The dietary risk assessment reported in ERC2012-01, *Sedaxane* has been updated to support subsequent use expansions of sedaxane and for the revision to the acceptable daily intake (ADI).

Aggregate chronic dietary intake estimates (food plus drinking water) revealed that the general population and infants less than one year old, the subpopulation which would ingest the most sedaxane relative to body weight, are expected to be exposed to less than 2% of the acceptable daily intake. Based on these estimates, the chronic (non-cancer) dietary risk from sedaxane is not of health concern for all population subgroups. The lifetime cancer risk was also not of health concern.

Aggregate acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than 2% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was all infants (<1 year old).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The final storage stability studies for sedaxane residues on crop and processed commodities submitted are adequate and support the intervals and conditions under which samples from the crop field trial and processing studies were stored. The MRLs established for sedaxane do not need to be revised. Refer to the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage for a list of the MRLs established for sedaxane.

Occupational Risks From Handling Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment.

Occupational risks are not of concern when Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment are used according to the registered label directions, which include protective measures.

Workers treating seed with Vibrance 500FS Seed Treatment or Vibrance XL Seed Treatment in commercial seed treatment operations, workers treating seed on-farm and workers planting treated seed can come into direct contact with sedaxane residues on the skin and through inhalation. Therefore, the label specifies that workers treating and handling treated seed must wear the following personal protective equipment (PPE). For commercial seed treatment, workers treating, bagging, sewing, stacking, and forklifting treated seed must wear cotton coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. In addition, workers cleaning commercial seed treatment equipment must wear chemical-resistant coveralls

over a long-sleeved shirt and long pants and chemical-resistant gloves. Workers treating on-farm and/or planting treated seed must wear cotton coveralls or a long-sleeved shirt, long pants and chemical-resistant gloves. For good hygiene purposes, it is also recommended for workers to wear a NIOSH-approved dust mask during all job activities. Closed transfer is required for commercial seed treatment of barley, wheat, oats, rye, triticale, buckwheat, millet (pearl and proso), teosinte, and wild rice. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Sedaxane Is Introduced Into the Environment?

Sedaxane is not expected to pose unacceptable risks to non-target organisms when used as directed on the label.

When sedaxane is introduced into the environment as a seed treatment it will adsorb to soil or be taken up into growing plants. Based on the physical-chemical properties of sedaxane and environmental fate data, limited movement in soil is expected and leaching into groundwater or runoff into surface water is not predicted. Although birds and mammals may be exposed to sedaxane if they feed on treated seed, a risk assessment has shown that sedaxane poses practically no risk to birds or mammals, even if a high amount of treated seed is ingested. Although sedaxane is moderately to highly toxic to aquatic organisms, when sedaxane is used as a seed treatment, limited exposure to the aquatic environment is expected. Sedaxane is expected to pose negligible risk to bees from contact and oral exposure. Risks to beneficial arthropods are expected to be negligible.

Value Considerations

What Is the Value of Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment?

Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment are end-use products that are effective in the control or suppression of seed and soil-borne diseases in crops.

Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment provide effective solutions to manage commercially important diseases such as rots (seed, root, crown, and foot), seedling blights, damping-off, seed-borne septoria, smuts, bunts and take-all. The multiple modes of fungicidal action found in Vibrance XL Seed Treatment provide benefits in terms of disease resistance management along with increased spectrum of disease protection. Moreover, because of recommended tank-mixes on the product labels, these products provide options for simultaneous management of certain insect pests and fungal diseases.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment on the skin or through inhalation of spray mists and dust, the labels specify that workers treating and handling treated seed must wear the following PPE. For commercial seed treatment, workers treating, bagging, sewing, stacking, and forklifting treated seed must wear cotton coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. In addition, workers cleaning commercial seed treatment equipment must wear chemical-resistant coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. Workers treating on-farm and/or planting treated seed must wear cotton coveralls or a long-sleeved shirt, long pants and chemical-resistant gloves. For good hygiene purposes, it is also recommended for workers to wear a NIOSH-approved dust mask during all job activities. Closed transfer is required for commercial seed treatment of barley, wheat, oats, rye, triticale, buckwheat, millet (pearl and proso), teosinte, and wild rice.

Next Steps

Before making a final registration decision on sedaxane, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency’s response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on sedaxane (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

Science Evaluation

Sedaxane

1.0 The Active Ingredient, Its Properties and Uses

Please refer to Evaluation Report ERC2012-01, *Sedaxane* for the complete chemistry review of sedaxane and its associate end-use products, as well as the directions for use and mode of action.

2.0 Methods of Analysis

Please refer to ERC2012-01, *Sedaxane* for a summary of the analytical methods previously reviewed for sedaxane.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

For the original toxicology review of sedaxane, please see ERC2012-01, *Sedaxane*. Two data requirements were identified during the original review, a short-term inhalation study as well as ovarian follicle and corpora lutea counts in the low and mid doses in the two-generation reproductive toxicity study.

A waiver request was received for the requirement for a short-term inhalation toxicity study in rats. The waiver request was found to be acceptable and the study is no longer considered required data. Outstanding data concerning ovarian follicle and corpora lutea counts at low and mid dose levels in the two-generation reproductive toxicity study in rats were received and showed no effects from sedaxane exposure. A reproductive toxicity NOAEL was established for females. The risk assessment has been updated. All toxicity data requirements have now been satisfied.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Incidents were searched and reviewed for the active sedaxane. As of August 20, 2014, there were three incident reports involving sedaxane in the PMRA database, two human and one domestic animal.

The two human incidents occurred in Canada. They were classified as either minor or moderate in severity and involved exposure to seeds treated with various active ingredients including sedaxane. The skin and eye irritation effects experienced by one individual were found to be associated with the reported exposure scenario (i.e. potential dermal contact with treated seed dust). In laboratory animals, sedaxane was not irritating to the skin and it was minimally irritating to the eyes. Additionally, sedaxane only accounts for a small percentage of the product formulation and it was therefore unlikely to be the reason behind the irritation in the incident reports.

The domestic animal incident involving sedaxane was reported from the United States. The cow affected in this report died following ingestion of cereal grains treated with various pesticides including sedaxane.

No changes to the risk assessment are required based on the available incident reports.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential 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. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for sedaxane. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young compared to parental animals in the reproductive toxicity study. Vaginal opening was delayed and anogenital distance was increased in female offspring at the highest dose tested; however, these effects were marginal, occurring in the presence of maternal toxicity (liver, ovary and body weight effects) and were not considered to represent a serious effect. There were no treatment-related effects in the rat developmental toxicity study. A marginally increased incidence of late abortions was observed at the highest dose tested in the rabbit developmental toxicity study. Although abortions are considered a serious developmental endpoint, the level of concern was tempered by the presence of maternal toxicity (body weight loss, decreased or no food consumption, reduced defecation), the low incidence of this finding, and the singular incidences of abortions in the laboratory's historical control database. The NOAEL of 100 mg/kg bw/day for abortions in the rabbit developmental toxicity study was considered to be a conservative endpoint and is considered to be sufficiently conservative to account for seriousness of the endpoint. Overall, there is a low concern for sensitivity of the young and effects on the young are well-characterized. Therefore, the *Pest Control Products Act* factor has been reduced to 1-fold.

3.2 Acceptable Daily Intake (ADI)

To estimate risk of repeat dietary exposure, the 2-year combined chronic/oncogenicity study in rats with a NOAEL of 11 mg/kg bw/day was selected for risk assessment. At 67 mg/kg bw/day, increased liver weight, eosinophilic cell foci and hepatocellular hypertrophy, increased thyroid follicular cell hypertrophy and epithelial desquamation, increased thyroid basophilic colloid and decreased hind limb grip strength were observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100-fold.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{POD}}{\text{CAF}} = \frac{11 \text{ mg/kg bw/day}}{100} = 0.1 \text{ mg/kg bw/day of sedaxane}$$

3.3 Occupational Risk Assessment

3.3.1 Toxicological Endpoints

Occupational exposure to Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

Short-, Intermediate-Term Dermal

For short- and intermediate-term dermal risk assessment for adults, the 90-day dietary toxicity study in rats was selected. The existing short-term dermal toxicity study did not address the endpoint of concern thus necessitating the use of an oral study for risk assessment. At 168 mg/kg bw/day, decreased forelimb/hindlimb grip strength and decreased body weight, body weight gain and food consumption were observed. The NOAEL was 24.8 mg/kg bw/day.

For occupational scenarios, the target Margin of Exposure (MOE) selected for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-, Intermediate-Term Inhalation

For short- and intermediate-term inhalation risk assessment for adults, the 90-day dietary toxicity study in rats was selected. An acceptable scientific waiver rational was received for the short-term inhalation study requirement and therefore, an oral study was used for risk assessment. At 168 mg/kg bw/day, decreased forelimb/hindlimb grip strength and decreased body weight, body weight gain and food consumption were observed. The NOAEL was 24.8 mg/kg bw/day.

For occupational scenarios, the target MOE selected for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Other endpoints as discussed in ERC2012-01, *Sedaxane* remain the same. All endpoints are listed in Appendix I, Table 1.

3.3.1.1 Dermal Absorption

Refer to ERC2012-01, *Sedaxane* for the dermal absorption of sedaxane.

3.3.2 Occupational Exposure and Risk

Vibrance 500FS Seed Treatment is registered for commercial (closed transfer) and on-farm seed treatment of small grain cereals: barley, wheat, oats, rye, triticale, buckwheat, millet (pearl and proso), teosinte, wild rice. It is registered for commercial seed treatment only (open and closed transfer) of Crop Subgroup 20A (rapeseed), corn and sorghum. It is also registered for commercial (open and closed transfer) and on-farm seed treatment of Crop Subgroup 6C (dried shelled peas and beans) and soybeans.

3.3.2.1 Commercial Seed Treatment Exposure and Risk Assessment

Individuals have potential for exposure to sedaxane while treating seed in commercial seed treatment facilities and by commercial mobile treaters. Chemical specific data for assessing human exposure during commercial seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers in commercial seed treatment settings.

3.3.2.1.1 Crop Subgroup 20A, Soybean, Crop Subgroup 6C, Corn and Sorghum

Vibrance 500FS Seed Treatment is registered for commercial seed treatment of Crop Subgroup 20A, soybean, Crop Subgroup 6C, corn and sorghum using open or closed transfer systems.

For assessing seed treatment in low-capacity commercial facilities, the surrogate study used in the risk assessment was conducted in open pour commercial facilities. In the study, workers were treating soybean seed with Apron FL, containing metalaxyl, at a target rate of 30 g a.i./100 kg seed. The average replicate length was approximately three hours. The following tasks were monitored: mixer/operator, bagger, and bag sewer. Three replicates were monitored per task. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath long clothes. All workers wore one layer of clothing and some wore more layers for warmth. Mixer/operators also wore goggles, chemical-resistant gloves and aprons. Baggers wore thick cotton gloves for warmth. Some workers wore dust masks. Inhalation exposure for each worker was measured by means of a personal air sampling pump with a sampler consisting of a

XAD-2 vapour collection tube and two glass fibre filters. Exposure values were normalized for the amount of active ingredient handled. The 90th percentile values from the Apron FL study were used in the risk assessment because of study limitations (small sample sizes, clothing and QA/QC irregularities).

For assessing seed treatment in high-capacity seed treatment operations, the surrogate study used in the risk assessment was conducted in five Canadian large closed-transfer commercial seed treatment facilities. In the study, workers were treating canola seed with Helix 289 FS, containing thiamethoxam, at a target rate of 400 g a.i./100 kg seed. The average replicate length was approximately 9.65 hours. The following tasks were monitored: treating (n = 17), cleaning, bagging/sewing/stacking (n = 53) and forklift driving (n = 12). Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Treaters and cleaners wore chemical-resistant coveralls over a single layer and chemical-resistant gloves. Forklift drivers and bagger/sewer/stackers wore cotton coveralls over a single layer and chemical-resistant gloves. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an OSHA Versatile Sampler (OVS) tube. Exposure values for treaters and bagger/sewer/stackers were normalized for the amount of active ingredient handled. Exposure values for cleaners were normalized for the application rate used in the study. However, it is uncertain that the normalized values are applicable for the Vibrance 500FS Seed Treatment risk assessment, since there is a 80-fold difference between the application rates of the study (400 g a.i./100 kg seed) and the use of Vibrance 500FS Seed Treatment (5 g a.i./100 kg). Therefore, risk estimates for cleaners were calculated using both the non-normalized and normalized exposure values from the Helix study. For the Helix study, all phases were well conducted and reported and no significant limitations were identified. As such, arithmetic mean values were considered adequate for use in risk assessments.

Dust off data showed that canola seed treated with Vibrance 500FS Seed Treatment and Helix Xtra were comparably dusty to the seed used in the two surrogate studies (soybean seed treated with Apron FL and canola seed treated with Helix Xtra). These data may be extrapolated to the rest of Crop Subgroup 20A, as all rapeseed cultivars have equivalent seed morphology and are treated and handled in the same manner in commercial seed treatment. In addition, the dust off data showed that soybean seed treated with Vibrance 500FS Seed Treatment were less dusty than canola seed treated with Helix Xtra and comparably dusty to soybean seed treated with Apron FL. For corn, Vibrance 500FS Seed Treatment-treated seed had similar dust off potential to Apron FL-treated soybean seed and Helix XTra-treated canola seed. For sorghum, due to the relatively small market, seeds are either not treated with a seed treatment product or are treated in the United States and imported into Canada. As such, no dust off data were produced for sorghum seed. Considering the morphological and agricultural similarities between sorghum and corn, it is not expected that the dust off of sorghum would be substantially more than the dust off of corn. As such, the surrogate studies are not expected to underestimate exposure of the use from Vibrance 500FS Seed Treatment on Crop Subgroup 20A, soybean, corn and sorghum.

Treated dry beans (with Apron Maxx RTA or with Apron Maxx RTA and Vibrance 500FS Seed Treatment) were less dusty than Apron FL-treated soybeans and Helix Xtra-treated canola. However, untreated dry beans were dustier than the seeds used in the surrogate studies. (Untreated light red kidney beans were approximately five times dustier.) As such, the use of the surrogate studies to conduct the commercial seed treatment risk assessment for Crop Subgroup 6C may underestimate risk.

Seed treating capacities were derived from commercial throughput values for corn, soybean, and canola based on survey data from the Agricultural Handlers Exposure Task Force (AHETF). These representative crops are expected to have the largest amount treated per day commercially in Canada and are not likely to underestimate treating capacities for the other seed types identified on the label. Canola values were used to cover Crop Group 20A seeds, soybean values were used for soybean and Crop Subgroup 6C seeds, and corn values were used for corn and sorghum seeds.

Table 3.3.2.1.1A presents the non-cancer risk estimates for the commercial seed treatment of Crop Subgroup 20A, soybean, Crop Subgroup 6C, corn and sorghum with Vibrance 500FS Seed Treatment. Calculated MOEs were well above the target MOE of 100.

Table 3.3.2.1.1A Non-cancer risk estimates for workers involved with commercial seed treatment Crop Subgroup 20A, soybean, Crop Subgroup 6C, corn and sorghum

Worker task	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[3]	Exposure (mg/kg bw/day)[4,5]	Calculated MOE[6]
	Dermal	Inhalation	Total[2]				
Small-scale open transfer commercial treatment (using Apron FL study unit exposure values)							
Crop Subgroup 20A (canola/rapeseed)							
Mixer/operator	211.49	4.85	19.65	0.00005	67000	8.23×10^{-4}	30100
Bagger	40.14	2.3	5.11	0.00005	67000	2.14×10^{-4}	116000
Bagger sewer	96.1	37.21	43.94	0.00005	67000	1.84×10^{-3}	13500
Soybean and Crop Subgroup 6C (dried shelled peas and beans)							
Mixer/operator	211.49	4.85	19.65	0.00005	63000	7.74×10^{-4}	32000
Bagger	40.14	2.3	5.11	0.00005	63000	2.01×10^{-4}	123000
Bagger sewer	96.1	37.21	43.94	0.00005	63000	1.73×10^{-3}	14300
Corn and sorghum							
Mixer/operator	211.49	4.85	19.65	0.00005	125000	1.54×10^{-3}	16200
Bagger	40.14	2.3	5.11	0.00005	125000	3.99×10^{-4}	62100
Bagger sewer	96.1	37.21	43.94	0.00005	125000	3.43×10^{-3}	7230
Large-scale closed transfer commercial treatment (using Helix study unit exposure values)							
Crop Subgroup 20A (canola/rapeseed)							
Treater (CRC)	7.36	0.27	0.785	0.00005	67000	3.29×10^{-5}	754000
Cleaner – not normalized	19.4	1.54	2.90	0.00005	67000	2.90×10^{-3}	8560
Cleaner – normalized	4.84×10^{-2}	3.84×10^{-3}	7.23×10^{-3}	0.00005	67000	3.61×10^{-5}	686000
Bagger/sewer/stacker	1.29	0.25	0.340	0.00005	67000	1.43×10^{-5}	1740000
Forklift operator	0.72	0.105	0.155	0.00005	67000	6.51×10^{-6}	3810000

Worker task	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[3]	Exposure (mg/kg bw/day)[4,5]	Calculated MOE[6]
	Dermal	Inhalation	Total[2]				
Soybean and Crop Subgroup 6C (dried shelled peas and beans)							
Treater	7.36	0.27	0.785	0.00005	63000	3.09×10^{-5}	802000
Cleaner – not normalized	19.4	1.54	2.90	0.00005	63000	2.90×10^{-3}	8560
Cleaner – normalized	4.84×10^{-2}	3.84×10^{-3}	7.23×10^{-3}	0.00005	63000	3.61×10^{-5}	686000
Bagger/sewer/stacker	1.29	0.25	0.340	0.00005	63000	1.34×10^{-5}	1850000
Forklift operator	0.72	0.105	0.155	0.00005	63000	6.12×10^{-6}	4050000
Corn and sorghum							
Treater	7.36	0.27	0.785	0.00005	125000	6.13×10^{-5}	404000
Cleaner – not normalized	19.4	1.54	2.90	0.00005	125000	2.90×10^{-3}	8560
Cleaner – normalized	4.84×10^{-2}	3.84×10^{-3}	7.23×10^{-3}	0.00005	125000	3.61×10^{-5}	686000
Bagger/sewer/stacker	1.29	0.25	0.340	0.00005	125000	2.66×10^{-5}	933000
Forklift operator	0.72	0.105	0.155	0.00005	125000	1.21×10^{-5}	2040000

[1] For small scale open transfer commercial treatment, the 90th percentile values of the Apron FL study on soybean seed were used. For large scale closed transfer commercial treatment, the arithmetic mean values were used from the Helix study.

[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure

[3] Mean-peak seed throughputs from the AHETF Seed Treatment Survey 2011-2012

[4] For mixer/operator, bagger, bagger sewer, treater, bagger/sewer/stacker, and forklift operator:
Exposure = Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)

[5] Not normalized cleaner unit exposure values are in µg/kg bw/day; exposure = (Total unit exposure)/(1000 µg/mg)
Normalized cleaner unit exposure values are in (µg/kg bw/ g a.i./100kg seed); as such,
exposure = (Total unit exposure × 5 g a.i./100 kg seed)/(1000 µg/mg)

[6] Based on POD = 24.8 mg /kg bw/day, target MOE = 100

A cancer potency factor (q_1*) was identified and, therefore, a cancer risk assessment was required for occupational exposure. Cancer risk is estimated by extrapolating the average daily dose (ADD) over an average lifetime worked to obtain a lifetime average daily dose (LADD). The LADD is compared to the cancer potency factor to determine the cancer risk.

From the non-cancer risk assessment, exposure from corn seed treatment results in the highest potential risk. In addition, according to the AHETF survey, corn has the longest commercial treating period compared to the other registered crops; this is considered a conservative estimate for corn seed treatment in Canada since the survey for corn was conducted in the United States only, which is expected to have a longer treating period. As such, the cancer risk from corn represents the highest among the registered crops. Individuals are expected to work a maximum of 206 days per year (maximum duration for corn) and may work up to 40 years in commercial seed treatment. A risk below 1×10^{-5} is considered acceptable in worker populations.

Table 3.3.2.1.1B presents the cancer risk estimates for the commercial seed treatment of corn seeds with Vibrance 500FS Seed Treatment, which were well below 1×10^{-5}.

Table 3.3.2.1.1B Cancer risk estimates for workers involved with commercial corn seed treatment

Worker task	Total unit exposure (µg/kg a.i. handled)[1]	App rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[2]	ADD (mg/kg bw/day)[3,4]	LADD (mg/kg bw/day)[5]	Cancer Risk[6]
Small-scale open transfer commercial facilities (using Apron FL study unit exposure values)						
Mixer/operator	19.65	0.00005	90000	1.11×10^{-3}	3.20×10^{-4}	1.22×10^{-6}
Bagger	5.11	0.00005	90000	2.87×10^{-4}	8.32×10^{-5}	3.17×10^{-7}
Bagger sewer	43.94	0.00005	90000	2.47×10^{-3}	7.15×10^{-4}	2.73×10^{-6}
Large-scale closed transfer commercial facilities (using Helix study unit exposure values)						
Treater	0.785	0.00005	90000	4.42×10^{-5}	1.28×10^{-5}	4.87×10^{-8}
Cleaner – not normalized	2.90	0.00005	90000	2.90×10^{-3}	8.39×10^{-4}	3.20×10^{-6}
Cleaner – normalized	7.23×10^{-3}	0.00005	90000	3.61×10^{-5}	1.05×10^{-5}	3.99×10^{-8}
Bagger/sewer/stacker	0.340	0.00005	90000	1.91×10^{-5}	5.54×10^{-6}	2.11×10^{-8}
Forklift operator	0.155	0.00005	90000	8.74×10^{-6}	2.53×10^{-6}	9.64×10^{-9}

[1] "Total unit exposure" from Table 3.3.2.1.1A

[2] Mean-normal seed throughputs from the AHETF Seed Treatment Survey 2011-2012

[3] For mixer/operator, bagger, bagger sewer, treater, bagger/sewer/stacker, and forklift operator:
ADD = Average daily dose = Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)

[4] Not normalized cleaner unit exposure values are in µg/kg bw/day; ADD = (Total unit exposure)/(1000 µg/mg)
Normalized cleaner unit exposure values are in (µg/kg bw/ g a.i./100kg seed); as such,
ADD = (Total unit exposure × 5 g a.i./100 kg seed)/(1000 µg/mg)

[5] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{206 working days per year} \times \text{40 years of exposure)}}{\text{(365 days/year} \times \text{78 years in lifetime)}}$

[6] Based on $q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

As noted in both non-cancer and cancer risk assessments, all calculated MOEs were well above the target MOE of 100 and cancer risk estimates were well below 1×10^{-5}. Therefore, although Crop Subgroup 6C seeds may be dustier than the seeds from the surrogate studies and no dust off data for sorghum seed were provided, no additional dust off data are required. No risks of concern were identified for commercial seed treatment of Crop Subgroup 20A, soybean, Crop Subgroup 6C, corn and sorghum.

3.3.2.1.2 Small Grain Cereals (Barley, Wheat, Oats, Rye, Triticale, Buckwheat, Millet [Pearl and Proso], Teosinte and Wild Rice)

Vibrance 500FS Seed Treatment is registered for commercial seed treatment of barley, wheat, oats, rye, triticale, buckwheat, millet (pearl and proso), teosinte and wild rice. Vibrance XL Seed Treatment is registered for commercial seed treatment of barley, wheat, oats, rye, and triticale. Commercial seed treatment of small grain cereals of sedaxane is restricted to closed transfer operations only.

For assessing commercial treatment of small grain cereal seed, the surrogate study used in the risk assessment was conducted in closed-transfer commercial facilities. In the study, workers were treating wheat seed with Jockey Fungicide, containing fluquinconazole and prochloraz, at target rates of 75 and 14 g a.i./100 kg seed, respectively. The monitoring period for treaters (n = 7) and cleaners (n = 8) was less than 35 minutes, whereas the monitoring period for baggers (n =

22) ranged from 3 to 8 hours. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Treaters wore a long-sleeved shirt, long pants and nitrile gloves. Cleaners wore Tyvek coveralls over a long-sleeved shirt, long pants and nitrile gloves. Baggers wore a long-sleeved shirt and long pants. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an IOM multi-dust sampler with a glass fibre filter. Exposure values for treaters and baggers were normalized for the amount of active ingredient handled. Exposure values for cleaners were normalized for the application rate used in the study. Since the application rates from the study (14 g a.i./100 kg seed) and for the proposed use (5 g a.i./100 kg) are similar, risk estimates for cleaners were calculated using normalized exposure values from the Jockey study. In addition, cleaner exposure was monitored for only 9 – 33 minutes in the study; as such, the risk estimates for cleaner and treater were combined to take into account workers who conduct both tasks during the workday. For the Jockey study, the arithmetic mean was used for all activities since there were an adequate number of replicates and the recoveries were sufficient. The highest value of the two actives monitored in the surrogate study was chosen for risk assessment purposes since it should not underestimate exposure.

The submitted dust off studies did not measure dust off potential of Jockey-treated wheat seed. However, dust off potential of wheat seed treated with other formulations was measured. Vibrance 500FS Seed Treatment-treated barley and oat seed had higher dust off potential than Austral Plus Net-treated wheat seed (1.6x higher for barley and 3.4x higher for oats). The dust off potential for Vibrance XL Seed Treatment-treated barley seed was 5.4x lower than that for Austral Plus Net-treated wheat seed. In addition, the dust off potential for Vibrance XL Seed Treatment-treated oat seed is comparable to that of Austral Plus Net-treated wheat seed. No dust off data were submitted for rye, triticale, buckwheat, millet (pearl and proso), teosinte or wild rice. As such, the Jockey study may underestimate the exposure for the registered use of sedaxane on small grain cereal seed.

The treating capacity of small grain cereal seeds was derived from commercial throughput values for wheat based on survey data from the AHETF. Wheat as the representative crop is expected to have the largest amount treated per day commercially in Canada and is not likely to underestimate treating capacities for the other seed types identified on the label.

Tables 3.3.2.1.2A and 3.3.2.1.2B present the non-cancer and cancer risk estimates, respectively, for the commercial seed treatment of small grain cereals with Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment. The calculated MOEs were well above the target MOE of 100. Cancer risk for commercial workers treating cereal seed was estimated by calculating the LADD. Individuals are expected to work a maximum of 34 days per year (from the AHETF survey) and may work up to 40 years in commercial seed treatment for wheat. Calculated cancer risk estimates were well below 1×10^{-5}.

Dust off data for the surrogate study (wheat seed treated with Jockey) were not submitted and dust off potential of rye, triticale, buckwheat, millet (pearl and proso), teosinte and wild rice were not measured. However, dust off data were provided for wheat seed that was treated with

another product. In addition, all calculated MOEs were well above the target MOE of 100 and cancer risk estimates were well below 1×10^{-5}. As such, additional dust off data for small grain cereal seeds are not required. No risks of concern are expected for commercial seed treatment of small grain cereals.

Table 3.3.2.1.2A Non-cancer risk estimates for workers treating small grain cereal seed in commercial seed treatment operations

Worker task	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./kg seed)	Seed treated (kg seed/day)[3]	Exposure (mg/kg bw/day)[4,5]	Calculated MOE[5]
	Dermal	Inhalation	Total[2]				
Closed transfer commercial operations (using Jockey study unit exposure values)							
Small grain cereals (barley, wheat, oats, rye, triticale, buckwheat, millet [pearl and proso], teosinte and wild rice)							
Treater	0.88	0.016	0.078	0.00005	92000	4.46×10^{-6}	5560000
Bagger	17.67	0.89	2.127	0.00005	92000	1.22×10^{-4}	203000
Cleaner	18.46	0.64	1.93	0.00005	92000	1.11×10^{-4}	223000
Treater + Cleaner*	-	-	-	0.00005	92000	1.16×10^{-4}	214000

[1] For closed transfer commercial operations, the arithmetic mean values were used from the Jockey study
[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure
[3] Mean-peak seed throughputs from the AHETF Seed Treatment Survey 2011-2012
[4] For treater & bagger, exposure = (Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)
[5] Cleaner unit exposure values are in (µg/ g a.i./100kg seed); as such,
exposure = (Total unit exposure × 5 g a.i./100 kg seed)/(80 kg bw × 1000 µg/mg)
[6] Based on POD = 24.8 mg /kg bw/day, target MOE = 100
* Assumes that a worker both treats and cleans in the same workday; exposure = treater exposure + cleaner exposure

Table 3.3.2.1.2B Cancer risk estimates for workers involved with commercial seed treatment of small grain cereals

Worker task	Total unit exposure (µg/kg a.i. handled)[1]	App rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[2]	ADD (mg/kg bw/day)[3,4]	LADD (mg/kg bw/day)[5]	Cancer Risk[6]
Closed transfer commercial operations (using Jockey study unit exposure values)						
Treater	0.078	0.00005	48000	2.33×10^{-6}	1.11×10^{-7}	4.24×10^{-10}
Bagger	2.127	0.00005	48000	6.38×10^{-5}	3.05×10^{-6}	1.16×10^{-8}
Cleaner	1.93	0.00005	48000	1.21×10^{-4}	5.77×10^{-6}	2.20×10^{-8}
Treater + Cleaner*	-	0.00005	48000	1.23×10^{-4}	5.89×10^{-6}	2.24×10^{-8}

[1] "Total unit exposure" from Table 3.3.2.1.2A
[2] Mean-normal seed throughputs from the AHETF Seed Treatment Survey 2011-2012
[3] For treater and bagger:
ADD = Average daily dose = Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)
[4] Not normalized cleaner unit exposure values are in µg/kg bw/day; ADD = (Total unit exposure)/(1000 µg/mg)
Normalized cleaner unit exposure values are in (µg/ g a.i./100kg seed); as such,
ADD = (Total unit exposure × 5 g a.i./100 kg seed)/(80 kg bw × 1000 µg/mg)
[5] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{34 working days per year} \times \text{40 years of exposure)}}{\text{(365 days/year} \times \text{78 years in lifetime)}}$

[6] Based on $q_1^* = 3.81 \times 10^{-3}$ (mg/kg bw/day)$^{-1}$
* Assumes that a worker both treats and cleans in the same workday; therefore, total exposure = treater exposure + cleaner exposure

3.3.2.2 On-Farm Seed Treatment Exposure

Individuals have potential for exposure to sedaxane while treating seed on-farm. Chemical specific data for assessing human exposure during on-farm seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers treating seed on-farm.

3.3.2.2.1 Small Grain Cereal Seeds (Barley, Wheat, Oats, Rye, Triticale, Buckwheat, Millet [Pearl and Proso], Teosinte and Wild Rice), Soybean, and Crop Subgroup 6C

Vibrance 500FS Seed Treatment is registered for on-farm treatment of barley, wheat, oats, rye, triticale, buckwheat, millet (pearl and proso), teosinte, wild rice, soybean, and Crop Subgroup 6C. Vibrance XL Seed Treatment is registered for on-farm treatment of barley, wheat, oats, rye, and triticale. Worker exposure was assessed for treating seed with open transfer systems.

For on-farm seed treatment and planting of treated seed, the Dividend 36FS study was considered appropriate to be used as a surrogate study in the risk assessment. The study measured 16 replicates treating and planting wheat seed on-farm. In all trials, wheat seed was treated with Dividend 36FS, containing difenoconazole, at a target rate of 24.8 g a.i./100 kg. Replicates were monitored for less than 3 hours to 8 hours. The product was open poured manually into the treatment equipment. Treated wheat seed was not bagged. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Workers wore a single layer and neoprene gloves. Inhalation exposure was monitored using OVS samplers attached to a personal air sampling pump. The study had minor limitations and had acceptable field recoveries and sample size. As such, the arithmetic mean values from the study were adequate for risk assessment purposes.

Submitted dust off data showed that Vibrance 500FS-treated soybean seed were less dusty than Dividend 36FS-treated wheat seed. In addition, both untreated dry bean seed and treated dry bean seed (with Apron Maxx RTA or with Apron Maxx RTA and Vibrance 500FS Seed Treatment) were less dusty than wheat seed treated with Dividend 36FS. Therefore, the use of the surrogate study is not expected to underestimate the risk from on-farm treating and planting soybean or Crop Subgroup 6C seeds.

In addition, barley seed treated with Vibrance 500FS Seed Treatment or Vibrance XL Seed Treatment were less dusty than wheat seeds treated with Dividend 36FS. The dust off data showed that oat seed treated with Vibrance 500FS Seed Treatment were comparably dusty to wheat seed treated with Dividend 36FS. Oat seed treated with Vibrance XL Seed Treatment were less dusty than wheat seed treated with Dividend 36FS. Therefore, the Dividend 36FS surrogate study is not expected to underestimate on-farm exposure for barley and oats. No dust off data were submitted for rye, triticale, buckwheat, millet (pearl and proso), teosinte or wild rice.

Seed treating capacities for on-farm treatment of small grain cereal, soybean and Crop Subgroup 6C seeds were derived from the PMRA default values. The amount handled for small cereal seeds was represented by the maximum value for planting of wheat at 13,500 kg seed planted per day. The amount handled for soybean seed was represented by the maximum value of planting of soybean at 9,000 kg seed planted per day. The amount handled for Crop Subgroup 6C seed was represented by the crop with the highest value within the subgroup: peas at 19,000 kg seed per day. These representative crops are expected to be the largest amount treated on-farm in Canada and are not likely to underestimate treating capacities for the other seeds types identified on the label.

Tables 3.3.2.2.1A and 3.3.2.2.1B present the non-cancer and cancer risk estimates, respectively, for the on-farm seed treatment of small grain cereal, soybean and Crop Subgroup 6C seeds with sedaxane. The calculated MOEs were well above the target MOE of 100. Cancer risk for on-farm workers treating seed was estimated by calculating the LADD. Individuals are expected to work a maximum of 10 days per year and may work up to 40 years in on-farm seed treatment. Calculated cancer risk estimates were well below 1×10^{-5}. As such, there are no risks of concern for on-farm seed treating and planting of small grain cereal, soybean and Crop Subgroup 6C seeds. Given the high MOEs and low cancer risk, it was determined that further confirmatory dust off data for rye, triticale, buckwheat, millet (pearl and proso), teosinte or wild rice are not required.

Table 3.3.2.2.1A Non-cancer risk estimates for workers on-farm treating and planting small grain cereal, soybean and Crop Subgroup 6C seeds

Crop	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./ kg seed)	Seed treated (kg seed/ day)[3]	Exposure (mg/kg bw/day)[4]	Calculated MOE[5]
	Dermal	Inhalation	Total[2]				
On-farm treating and planting (using Dividend 36FS study unit exposure values)							
Small grain cereals (barley, wheat, oats, rye, triticale, buckwheat, millet [pearl and proso], teosinte and wild rice)	407.34	223.03	251.54	0.00005	13500	2.12×10^{-3}	11700
Soybean	407.34	223.03	251.54	0.00005	9000	1.41×10^{-3}	17500
Crop Subgroup 6C (pulses)	407.34	223.03	251.54	0.00005	19000	2.99×10^{-3}	8300

[1] For on-farm treating and planting, the arithmetic mean values were used from the Dividend study
[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure
[3] Default PMRA Seed Treated Planted Per Day values
[4] Exposure = (Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)
[5] Based on POD = 24.8 mg /kg bw/day, target MOE = 100

Table 3.3.2.2.1B Cancer risk estimates for workers on-farm treating and planting small grain cereal, soybean and Crop Subgroup 6C seeds

Crop	Total unit exposure (µg/kg a.i. handled)[1]	App rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[2]	ADD (mg/kg bw/day)[3]	LADD (mg/kg bw/day)[4]	Cancer Risk[5]
On-farm treating and planting (using Dividend 36FS study unit exposure values)						
Small grain cereals	251.54	0.00005	13500	2.12×10^{-3}	2.98×10^{-5}	1.14×10^{-7}
Soybean	251.54	0.00005	9000	1.41×10^{-3}	1.99×10^{-5}	7.57×10^{-8}
Crop Subgroup 6C	251.54	0.00005	19000	2.99×10^{-3}	4.20×10^{-5}	1.60×10^{-7}

[1] "Total unit exposure" from Table 3.3.2.2.1A
[2] Default PMRA Seed Treated Planted Per Day values
[3] ADD = Average daily dose = Total unit exposure × App rate × Seed treated per day)/(80 kg bw × 1000 µg/mg)
[4] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{10 working days per year} \times \text{40 years of exposure)}}{\text{(365 days/year} \times \text{78 years in lifetime)}}$
[5] Based on $q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.3.2.3 Planting Exposure and Risk Assessment

Individuals have potential for exposure to sedaxane while planting treated seed. Chemical specific data for assessing human exposure during planting of treated seed were not submitted. As such, surrogate exposure data were used to estimate risk to workers planting treated seed.

3.3.2.3.1 Planting from Bagged Commercially Treated Seeds

3.3.2.3.1.1 Crop Subgroup 20A, Soybean, Crop Subgroup 6C, Corn and Sorghum

After commercial seed treatment with Vibrance 500FS Seed Treatment, Crop Subgroup 20A, soybean, and corn seed are bagged. In addition, some commercially treated Crop Subgroup 6C seed are bagged. Sorghum seed is not currently treated in Canada; therefore, planting of treated sorghum seeds is expected to be from bags. Workers load the treated seeds from bags into the planter.

To address planting exposure from bagged seed, the Gaucho planting study was used as a surrogate. In the study, 15 replicates were monitored while planting treated corn seed from bags. The seeds were treated with Gaucho FS 350 or Gaucho FS 600, containing imidacloprid. The workers in the study loaded treated seed from bags into the planter and sowed the seed using a closed cab tractor. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Workers wore a single layer and chemical-resistant gloves. Inhalation exposure was monitored using IOM samplers attached to a personal air sampling pump. The study was of good quality and had only minor limitations. As such, the arithmetic mean values from the study were adequate for risk assessment purposes.

Dust off data showed that canola seed treated with Vibrance 500FS Seed Treatment and Helix Xtra were significantly less dusty than Gaucho-treated corn seed. These data may be extrapolated to the rest of Crop Subgroup 20A, as all rapeseed cultivars have equivalent seed morphology and

are treated and handled in the same manner in commercial seed treatment. In addition, the dust off potential of soybean seed treated with Vibrance 500FS Seed Treatment, untreated dry bean seed, and treated dry bean seed (with Apron Maxx RTA or with Apron Maxx RTA and Vibrance 500FS Seed Treatment) was less than that of corn seed treated with Gaucho. Corn seed treated with Vibrance 500FS Seed Treatment were much less dusty than that treated with Gaucho. For sorghum, due to the relatively small market, seeds are either not treated with a seed treatment product or are treated in the United States and imported into Canada. As such, no dust off data were produced for sorghum seed. Considering the morphological and agricultural similarities between sorghum and corn, it is not expected that the dust off of sorghum would be substantially more than the dust off of corn. As such, the surrogate study is not expected to underestimate exposure of the use from Vibrance 500FS Seed Treatment on Crop Subgroup 20A, soybean, corn and sorghum.

Planting capacities for Crop Subgroup 20A, soybean, Crop Subgroup 6C, corn and sorghum seed were derived from the PMRA default values. The amount planted per day for each crop subgroup was chosen by selecting the crop within each group that has the maximum amount of seed planted per day on average. The amount planted per day for Crop Subgroup 20A came from canola (600 kg) and the amount for Crop Subgroup 6C came from peas (19,000 kg). The amount of seed planted per day for soybean and corn is 9,000 kg and 1,350 kg, respectively. The amount of seed planted for corn was used to represent that for sorghum. These representative crops are expected to be the largest amount planted in Canada and are not likely to underestimate planting amounts for the other seeds types identified on the label.

Tables 3.3.2.3.1.1A and 3.3.2.3.1.1B present the non-cancer and cancer risk estimates, respectively, for the planting of bagged seed commercially treated with sedaxane. The calculated MOEs were well above the target MOE of 100. Cancer risk for workers was estimated by calculating the LADD. Individuals are expected to work a maximum of 10 days per year and may work up to 40 years planting treated seed. Calculated cancer risk estimates were well below 1×10^{-5}. Considering the high MOEs and low cancer risk estimates, as well as the difference in dust off of the surrogate study seed and sedaxane-treated seed, it is expected that the risk from planting Vibrance 500FS-treated seed from bags in open cab tractors is not of concern.

Table 3.3.2.3.1.1A Non-cancer risk estimates for workers planting bagged commercially treated seed

Crop	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./ kg seed)	Seed planted (kg seed/day)[3]	Exposure (mg/kg bw/day)[4]	Calculated MOE[5]
	Dermal	Inhalation	Total[2]				
Planting bagged commercially treated seed (using Gaucho study unit exposure values)							
Crop Subgroup 20A	1515	82.83	188.88	0.00005	600	7.08×10^{-5}	350000
Soybean	1515	82.83	188.88	0.00005	9000	1.06×10^{-3}	23300
Crop Subgroup 6C	1515	82.83	188.88	0.00005	19000	2.24×10^{-3}	11100
Corn, sorghum	1515	82.83	188.88	0.00005	1350	1.59×10^{-4}	156000

[1] For planting commercial treated seed, the arithmetic mean values were used from the Gaucho study
[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure
[3] Default PMRA Seed Treated Planted Per Day values

[4] Exposure = (Total unit exposure × App rate × Seed planted per day)/(80 kg bw × 1000 µg/mg)
[5] Based on POD = 24.8 mg /kg bw/day, target MOE = 100

Table 3.3.2.3.1.1B Cancer risk estimates for workers planting bagged commercially treated seed

Crop	Total unit exposure (µg/kg a.i. handled)[1]	App rate (kg a.i./kg seed)	Seed planted (kg seed/ day)[2]	ADD (mg/kg bw/day)[3]	LADD (mg/kg bw/day)[4]	Cancer Risk[5]
Planting bagged commercially treated seed (using Gaucho study unit exposure values)						
Crop Subgroup 20A	188.88	0.00005	600	7.08×10^{-5}	9.95×10^{-7}	3.79×10^{-9}
Soybean	188.88	0.00005	9000	1.06×10^{-3}	1.49×10^{-5}	5.69×10^{-8}
Crop Subgroup 6C	188.88	0.00005	19000	2.24×10^{-3}	3.15×10^{-5}	1.20×10^{-7}
Corn, sorghum	188.88	0.00005	1350	1.59×10^{-4}	2.24×10^{-6}	8.53×10^{-9}

[1] "Total unit exposure" from Table 3.3.3.1.1A
[2] Default PMRA Seed Treated Planted Per Day values
[3] ADD = Average daily dose = Total unit exposure × App rate × Seed planted per day)/(80 kg bw × 1000 µg/mg)
[4] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{10 working days per year} \times \text{40 years of exposure)}}{\text{(365 days/year} \times \text{78 years in lifetime)}}$
[5] Based on $q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.3.2.3.2 Planting from Bulk Commercially Treated Seeds

3.3.2.3.2.1 Small Grain Cereals (Barley, Wheat, Oats, Rye, Triticale, Buckwheat, Millet [Pearl and Proso], Teosinte and Wild Rice) and Crop Subgroup 6C

Crop Subgroup 6C seed commercially treated with Vibrance 500FS Seed Treatment are bagged and planted as described in the previous section, or transferred to storage, grain truck or seed trailer and transferred by bulk into the planter. Small grain cereal seed treated with Vibrance 500FS Seed Treatment or Vibrance XL Seed Treatment are also transferred in bulk after treatment and then planted.

To address planting exposure from bulk seed, the Dividend XL RTA planting study was used as a surrogate. In the study, 18 workers were monitored during loading and planting treated wheat seeds with a liquid formulation, Dividend XL RTA Fungicide (containing difenoconazole and metalaxyl-M, where difenoconazole was the analyte of interest). The worker tasks monitored were multiple cycles of bulk loading of treated seed from bins or wagons into the seed tanks of a planter, followed by longer intervals of planting. All workers wore their own long-sleeved clothing over an inner full-body dosimeter, and most wore gloves when contacting equipment during loading, which were removed while inside tractor cabs. A few of the workers wore additional clothing items such as a jacket or thin coverall as a second clothing layer, or a dust mask during loading. Dermal dosimetry included inner whole-body dosimeters, hand washes and face/neck wipes. Inhalation monitoring utilized an OVS air sampling tube with XAD-2 sorbent attached to a personal air sampling pump. There were minor limitations in the study, and therefore, the arithmetic mean unit exposure values from this study are considered to be adequate to use for risk assessment purposes.

Dust off data showed that both untreated dry bean seed and treated dry bean seed (with Apron Maxx RTA or with Apron Maxx RTA and Vibrance 500FS Seed Treatment) were less dusty than wheat seeds treated with Dividend XL RTA. As such, the surrogate exposure study is not expected to underestimate the exposure from planting bulk Crop Subgroup 6C seed treated with Vibrance 500FS Seed Treatment.

The dust off potential of barley and oat seed treated with Vibrance XL Seed Treatment was less or comparable to that of wheat seed treated with Dividend XL RTA. However, barley and oat seed treated with Vibrance 500FS Seed Treatment were dustier than wheat seed treated with Dividend XL RTA. As mentioned previously, no dust off data were submitted for wheat, rye, triticale, buckwheat, millet (pearl and proso), teosinte or wild rice. Therefore, the use of the surrogate study may underestimate the risk from planting bulk commercially treated small grain cereal seed.

Planting capacities for small grain cereal and Crop Subgroup 6C seed were derived from the PMRA default values. The amount planted per day for each crop subgroup was chosen by selecting the crop within each group that has the maximum amount of seed planted per day on average. The amount planted per day for Crop Subgroup 6C came from peas (19,000 kg) and for small grain cereals came from wheat (13,500 kg). These representative crops are expected to have the largest amount planted per day in Canada and are not likely to underestimate planting amounts for the other seeds types identified on the label.

Tables 3.3.2.3.2.1A and 3.3.2.3.2.1B present the non-cancer and cancer risk estimates, respectively, for the planting of bulk seed commercially treated with sedaxane. The calculated MOEs were well above the target MOE of 100. Cancer risk for workers was estimated by calculating the LADD. Individuals are expected to work a maximum of 10 days per year and may work up to 40 years planting treated seed. Calculated cancer risk estimates were well below 1×10^{-5}. Considering the high MOEs and low cancer risk estimates, confirmatory dust off data for the other small grain cereal seeds are not required, and it is expected that the risk from planting bulk sedaxane-treated seed in open cab tractors is not of concern.

Table 3.3.2.3.2.1A Non-cancer risk estimates for workers planting bulk seeds commercially treated with sedaxane

Crop	Unit exposure (µg/kg a.i. handled)[1]			App rate (kg a.i./kg seed)	Seed planted (kg seed/day)[3]	Exposure (mg/kg bw/day)[4]	Calculated MOE[5]
	Dermal	Inhalation	Total[2]				
Planting bulk commercially treated seed (using Dividend XL RTA study unit exposure values)							
Small grain cereals	336	119	142.52	0.00005	13500	1.20×10^{-3}	20623
Crop Subgroup 6C	336	119	142.52	0.00005	19000	1.69×10^{-3}	14700

[1] For planting bulk treated seed, the arithmetic mean values were used from the Dividend XL RTA study
[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure
[3] Default PMRA Seed Treated Planted Per Day values
[4] Exposure = (Total unit exposure × App rate × Seed planted per day)/(80 kg bw × 1000 µg/mg)
[5] Based on POD = 24.8 mg /kg bw/day, target MOE = 100

Table 3.3.2.3.2.1B Cancer risk estimates for workers planting bulk seeds commercially treated with sedaxane

Crop	Total unit exposure (µg/kg a.i. handled)[1]	App rate (kg a.i./kg seed)	Seed planted (kg seed/ day)[2]	ADD (mg/kg bw/day)[3]	LADD (mg/kg bw/day)[4]	Cancer Risk[5]
Planting bulk commercially treated seed (using Dividend XL RTA study unit exposure values)						
Small grain cereals	142.52	0.00005	13500	1.20×10^{-3}	1.69×10^{-5}	6.44×10^{-8}
Crop Subgroup 6C	142.52	0.00005	19000	1.69×10^{-3}	2.38×10^{-5}	9.06×10^{-8}

[1] "Total unit exposure" from Table 3.3.3.2.1A
[2] Default PMRA Seed Treated Planted Per Day values
[3] ADD = Average daily dose = Total unit exposure × App rate × Seed planted per day)/(80 kg bw × 1000 µg/mg)
[4] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{10 working days per year} \times \text{40 years of exposure)}}{\text{(365 days/year} \times \text{78 years in lifetime)}}$
[5] Based on $q_1^* = 3.81\text{x}10^{-3}$ $(\text{mg/kg bw/day})^{-1}$

3.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal when planting treated seed.

3.4 Food Residues Exposure Assessment

3.4.1 Residues in Plant and Animal Foodstuffs

Refer to ERC2012-01, *Sedaxane* for a summary of the residue data previously reviewed and the rationale for the regulatory decision. The information captured herein relates to the final freezer storage stability studies for sedaxane residues in crop and processed commodities.

3.4.2 Dietary Risk Assessment

The dietary risk assessment reported in ERC2012-01, *Sedaxane* has been updated to support subsequent use expansions of sedaxane and the revision to the ADI.

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.4.2.1 Chronic (Non-Cancer) Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for sedaxane: 100% crop treated, default processing factors (where available) and maximum residue limits (MRLs) for all commodities. The basic chronic (non-cancer) dietary exposure from all registered sedaxane food uses (alone) for the total population, including infants and children, and all

representative population subgroups is less than 1% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to sedaxane from food and drinking water is 0.5% (0.0005 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 1.2% (0.001 mg/kg bw/day) of the ADI.

The following criteria were applied to the refined chronic cancer risk assessment: 100% crop treated, default (where available) and experimental processing factors (potato, dry and chips), the median residue for potato commodities and the MRLs for all livestock commodities. The lifetime cancer risk from exposure to sedaxane in food and drinking water was estimated to be 1.8×10^{-6} for the general population, which is not of health concern in view of the fact that the assessment was conducted with conservative criteria for estimates of food intake and drinking water as detailed below:

- The main conservatism in the estimate of food intake is that the amount of potential crop to be treated was considered to be 100%. At this level, the lifetime cancer risk from exposure to sedaxane in food (alone) was 5.6×10^{-7} for the general population, considerably below the level of concern (LOQ). Additionally, residues were <LOQ in all food commodities, except potato.
- The points contributing to the conservatism of the drinking water values are as follows. Mainly, the estimated environmental concentrations (EECs) used to determine drinking water estimates were calculated using conservative inputs with respect to application rate, timing and geographic scenario. Surface water modelling was not conducted, as run-off was expected to be minimal for the potato seed piece treatment. As well, the EEC values are based on a point of entry estimate, whereas the actual drinking water is expected to have lower residues than estimated, given the further dilution of water as it reaches the drinking water sources.

3.4.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic analysis for sedaxane: 100% crop treated, default processing factors (where available) and MRLs for all commodities. The basic acute dietary exposure (food alone) for all sedaxane registered commodities is estimated to be less than 1% of the acute reference dose (ARfD) for all population subgroups (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable, at less than 2% of the ARfD for all population subgroups (95^{th} percentile, deterministic); the highest exposed subgroup was all infants (<1 year old) at 1.1% of the ARfD (0.003 mg/kg bw).

3.4.3 Aggregate Exposure and Risk

The aggregate risk for sedaxane consists of exposure from food and drinking water sources only, as discussed in the previous section.

3.4.4 Maximum Residue Limits

MRLs established in Canada for sedaxane may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage.

4.0 Impact on the Environment

Please refer to ERC2012-01, *Sedaxane* for the complete environmental review for sedaxane.

ERC2012-01 incorrectly identified that sedaxane does not have systemic properties, however, sedaxane is a systemic fungicide.

Also, please note the following minor revision to Table 9 of ERC2012-01.

Risks to Terrestrial Organisms (Screening Level Assessment)

Organism	Exposure	Endpoint value	Uncertainty factor applied	EEC	RQ	LOC Exceeded
Invertebrates						
Bee	48h-Oral	>4.22 mg a.i./bee (4.73 kg a.i./ha)	1	0.0109 kg a.i./ha	2.3×10^{-03}	no oral exposure not expected

5.0 Value

Please refer to ERC2012-01, *Sedaxane* for the complete value review for sedaxane.

6.0 Pest Control Product Policy Considerations

Please refer to ERC2012-01, *Sedaxane* for the complete review of the Toxic Substances Management Policy considerations for sedaxane as well as the outcomes for the formulants and contaminants of health or environmental concern for the associated end-use products.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for sedaxane is comprehensive. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to sedaxane. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Sedaxane did not cause immunosuppression in mice. While there were signs of potential neurotoxicity at high doses, there was no evidence of a selective effect on the nervous system. In short-term and long-term studies on laboratory animals, the primary targets were the liver, thyroid and circulatory system.

There was no evidence that sedaxane was genotoxic; however, there was evidence of oncogenicity in mice and rats after chronic dosing. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residues in plants and animals is adequately understood. Refer to ERC2012-01, *Sedaxane* for information pertaining to the residue definition. The approved uses of sedaxane do not constitute a risk of concern for chronic (cancer and non-cancer) or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to establish maximum residue limits to protect human health.

Workers treating seed with Vibrance 500FS Seed Treatment or Vibrance XL Seed Treatment and workers planting treated seed are not expected to be exposed to levels of sedaxane that will result in health risks of concern when Vibrance 500FS Seed Treatment and Vibrance XL Seed Treatment are used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

7.2 Environmental Risk

Please refer to ERC2012-01, *Sedaxane* for the complete environmental review for sedaxane.

7.3 Value

Please refer to ERC2012-01, *Sedaxane* for the complete value review for sedaxane.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sedaxane Technical, Vibrance 500FS Seed Treatment (containing the technical grade active ingredient sedaxane) and Vibrance XL Seed Treatment (containing the technical grade active ingredients sedaxane, difenconazole and metalaxyl-m) to be used on seed from various crops to control or suppress soil and seed-borne diseases of seedlings and mature plants.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
ADD	average daily dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
App	application
ARfD	acute reference dose
ADD	average daily dose
bw	body weight
CAF	composite assessment factor
EEC	estimated environmental concentration
FDA	Food and Drugs Act
g	gram(s)
IOM	Institute of Occupational Medicine
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LOQ	limit of quantitation
mg	milligram(s)
MOE	margin of exposure
MRL	maximum residue limit
n	number of test subjects
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
OVS	OSHA Versatile Sampler
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
POD	point of departure
PPE	personal protective equipment
TRR	total radioactive residue
q_1*	lifetime adjusted unit risk potency factor for cancer
QA/QC	quality assurance and/or quality control

Appendix I Tables and Figures

Table 1 Toxicity Profile of Technical Sedaxane, Updated Entry for Two-Generation Reproductive Toxicity Study

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/ Animal/PMRA#	Study Results
2-generation reproduction (dietary) Wistar rats PMRA #1897908	**Parental toxicity:** NOAEL = 41/46 mg/kg bw/day ♂/♀, LOAEL = 120/143 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↑ liver weight, ↑ centrilobular heptocellular hypertrophy; enlarged liver (♀) **Reproductive toxicity:** NOAEL = 120/46 mg/kg bw/day ♂/♀ LOAEL = not established/143 mg/kg bw/day ♂/♀ At 143 mg/kg bw/day, ↓ ovarian weight, ↓ primordial follicles (P), ↓ growing and antral follicles (F1), ↓ ovarian corpora lutea (P), ↑ lactational diestrous (♀) **Offspring toxicity:** NOAEL = 46 mg/kg bw/day ♂/♀ LOAEL = 143 mg/kg bw/day ♂/♀, based on ↓ pup bw, delayed vaginal patency (F1; equivocal), ↑ anogenital distance (♀; equivocal), ↑ liver weight (histopathology not conducted), ↓ spleen weight (histopathology not conducted) **Evidence of reproductive toxicity**

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Sedaxane

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute neurotoxicity study (rats)	NOAEL = 30 mg/kg bw Clinical signs, decreased body weight, body weight gain and food consumption in males. Clinical signs, decreased activity, reduced muscle tone and decreased locomotor activity in females.	100
	ARfD = 0.3 mg/kg bw		
Repeated dietary	2-year dietary toxicity study (rats)	NOAEL = 11 mg/kg bw/day Increased liver weight, eosinophilic cell foci and hepatocellular hypertrophy, increased thyroid follicular cell hypertrophy and epithelial desquamation, increased thyroid basophilic colloid and decreased hind limb grip strength were observed.	100

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
	ADI = 0.1 mg/kg bw/day		
Short-term to intermediate-term dermal[2] and inhalation[3]	90-day dietary toxicity study (rats)	NOAEL = 24.8 mg/kg bw/day Decreased forelimb/hindlimb grip strength and decreased body weight, body weight gain and food consumption.	100
Cancer	80-week oncogenicity study (mice) & 104/105-week chronic/oncogenicity study (rats)	Sedaxane exhibits oncogenic potential. There were treatment-related thyroid follicular cell tumours and hepatocellular tumours in male rats, uterine adenocarcinomas in female rats and hepatocellular tumours in male mice. An adjusted unit risk value (q_1*) of 3.81×10^{-3} $(mg/kg\ bw/day)^{-1}$, for uterine adenocarcinomas was used for the cancer risk assessment and is protective of the other tumour types.	

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor (7%) was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 3 Integrated Food Residue Chemistry Summary

FREEZER STORAGE STABILITY	PMRA # 2106188, 2106189

Plant matrices:

Wheat (grain and straw), spinach (leaves), soybean (seed), dried broad bean (seed), orange (fruit) and potato (tuber)

The freezer storage stability data indicate that residues of the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555 and CSCC210616 are stable at $\leq$-18°C for 24 months.

Orange (fruit), soybean (seed), and dried broad been (seed)

The freezer storage stability data indicate that residues of the metabolite CSCD465008 are stable at $\leq$-18°C for 24 months.

Wheat (flour, germ and bran), soybeans (meal, hulls and oil) and orange (dried pulp, juice and oil)

The freezer storage stability data indicate that residues of the sedaxane isomers SYN508210 and SYN508211, and the metabolite CSCD465008 (tested in soybean meal, hulls and oil only) are stable at approximately -18°C for 12 months.

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**		Sedaxane	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**		Sedaxane	
METABOLIC PROFILE IN DIVERSE CROPS		The metabolism of sedaxane was similar in soybean, wheat and Swiss chard.	
ANIMAL STUDIES			
ANIMALS		**Ruminant and Poultry**	
RESIDUE DEFINITION FOR ENFORCEMENT		Sedaxane	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Sedaxane	
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**		Yes	
FAT SOLUBLE RESIDUE		Yes, based on the log K_{ow} of 3.3. However, the TRRs did not concentrate in the fat samples analyzed from the goat and hen metabolism studies.	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
Basic chronic non-cancer dietary exposure analysis **ADI = 0.1 mg/kg bw/day** **Estimated chronic drinking water concentration = 15 µg/L**	**All infants < 1 year**	0.2	1.2
	Children 1–2 years	0.6	1.0
	Children 3 to 5 years	0.4	0.9
	Children 6–12 years	0.3	0.6
	Youth 13–19 years	0.2	0.4
	Adults 20–49 years	0.1	0.4
	Adults 50+ years	0.1	0.4
	Females 13-49 years	0.1	0.4
	Total population	0.2	0.5
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.3 mg/kg bw** **Estimated acute drinking water**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
	All infants < 1 year	0.22	1.1
	Children 1–2 years	0.39	0.68

concentration = 15 µg/L	**Children 3 to 5 years**	0.27	0.55
	Children 6–12 years	0.18	0.39
	Youth 13–19 years	0.11	0.28
	Adults 20–49 years	0.08	0.29
	Adults 50+ years	0.06	0.26
	Females 13-49 years	0.07	0.29
	Total population	0.15	0.36
Refined cancer dietary exposure analysis **q_1^* = 0.00381 (mg/kg bw/day)$^{-1}$** **Estimated chronic drinking water concentration = 15 µg/L**	**POPULATION**	**ESTIMATED LIFETIME CANCER RISK**	
		Food Alone	**Food and Water**
	Total population	6.0×10^{-7}	1.8×10^{-6}

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

MRLs established in Canada for sedaxane may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage.

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
2106188	2011, SYN524464 - Storage Stability of Residues of CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCD465008 and CSCC210616 in Plant Matrices, DACO: 7.3, IIA 6.1.1
2106189	2010, SYN524464 - Stability of SYN508210, SYN508211 and CSCD465008 in Processed Commodities During Frozen Storage Pending Analysis, DACO: 7.3, IIA 6.1.1
2359526	2013, SYN524464 - Two-Generation Reproduction Toxicity Study in the Han Wistar Rat (Including Amendment 1): Final Report Amendment 2, DACO: 4.5.1
1108518	1999, On Farm Exposure Operator Study with Dividend 36 FS Seed Treatment on Wheat, DACO: 5.4
1168258	1993, Worker Exposure to Apron Flowable While Treating Seed Commercially-Amendment#1, DACO: 5.4
1349637	2000, Occupational Risk Exposure Assessment for HELIX 289FS, DACO: 5.4
1571553	2007, Determination of Operator Exposure to Imidacloprid During Loading/Sowing of Gaucho Treated Maize Seeds Under Realistic Field Conditions in Germany and Italy, DACO: 5.4
1772278	2009, Fluquinconazole and Prochloraz: Determination of Operator Exposure During Cereal Seed Treatment With Jockey Fungicide in Germany, United Kingdom and France, DACO: 5.4
1898373	2009, SYN524464 FS (A16148C) - In Vivo Dermal Absorption Study in the Rat, DACO: 5.8, IIIA 7.6.1
1934640	2010, Sedaxane (SYN 524464): Laboratory Dust-Off Measurements of Canola, Soybean, and Cereal Seeds Treated with Sedaxane-Containing Formulations Treated with Sedaxane-Containing Formulations, DACO: 5.10, 5.6, 5.7, 5.9, IIIA 7.5.4
2200093	2011, Observational Monitoring of Dermal and Inhalation Exposure to Workers Planting Cereal Grain Seed Following Treatment with Dividend XL RTA Fungicide, DACO: 5.6
2212966	2012, Laboratory Dust-Off Data and Scientific Rationale in Support of the Registration of Vibrance 500FS Fungicide on Corn, Legumes (Crop Group 6C), Oilseed Rape (Crop Subgroup 20A), and Sorghum, DACO: 4.6.8, 4.7.7, 4.8, 5.14, IIIA 7.11