Registration Decision RD2020-16

Broflanilide, Cimegra, Teraxxa and Teraxxa F4

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Registration decision statement[1] for broflanilide

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 Broflanilide Technical Insecticide, Cimegra, Teraxxa and Teraxxa F4 containing the technical grade active ingredient broflanilide, to be used as a soil treatment to control wireworm in potatoes, and wireworm and corn rootworm in corn, and as a seed treatment to control wireworm in small cereal grains and wheat.

This decision is consistent with the Proposed Registration Decision, PRD2020-06, *Broflanilide, Cimegra, Teraxxa and Teraxxa F4*, which contains a detailed evaluation of the information submitted in support of this registration. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable. See Appendix I for a summary of comments received during the consultation process as well as Health Canada's response to these comments.

Other information

The relevant test data on which the decision is based (as referenced in PRD2020-06, Broflanilide, Cimegra, Teraxxa and Teraxxa F4 are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).

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

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

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

Appendix I Comments and responses

A. Toxicology assessment

1. Comments related to findings in the chronic toxicity/oncogenicity study in the rat

Comment:

The applicant commented that it was their opinion that the adrenal gland tumours observed in female rats in the 24-month chronic toxicity/oncogenicity study were not related to treatment, based on a "quantitative and biology-based review of the incidence data".

PMRA response:

At the highest dose tested in the 24-month dietary chronic toxicity/oncogenicity study in rats, there were two incidences (4%) of adrenal gland carcinoma in female rats, compared to zero incidences in all other groups including the control group. The mean incidence from control animals in historical studies was 0.2%, with a range of 0–2%. The incidence of this tumour type in the concurrent control group from the study was comparable to the historical control values provided, and the incidence in high-dose female rats exceeded the upper end of the historical control range. It remains the PMRA's conclusion that the increase in adrenal gland carcinoma at the highest dose tested in female rats was considered to be treatment-related given the rarity of this tumour as shown by the low historical incidence and considering the histopathology findings of the adrenal gland at the same and lower dose levels, which included vacuolization, hypertrophy, and fatty change.

Comment:

The applicant commented that the incidences of uterine adenocarcinoma observed in female rats in the 24-month chronic toxicity/oncogenicity study were within the laboratory historical control range and thus not of biological significance.

PMRA response:

Increases in the incidence of uterine adenocarcinoma were observed in females at the two highest dose levels tested in the 24-month chronic toxicity/oncogenicity study in rats, with incidences of 22% and 28% respectively, compared to 12% in the concurrent control group. Two sets of historical control data were provided for this tumour type. One set represented historical control incidences from studies conducted at the same laboratory that performed the 24-month chronic toxicity/oncogenicity study with broflanilide. The other historical control data set was less relevant to the evaluation of broflanilide, as the data were obtained from studies using animals from multiple breeders and from a different conducting laboratory. The incidence of uterine adenocarcinoma in the first set of historical control studies ranged from 2% to 20%, with a mean of 12%. Compared to the first set of historical control data, the incidence of this tumour type in control animals from the 24-month study with broflanilide was similar to the historical control mean, and the incidences in the two highest dose groups exceeded the upper end of the historical control range. It remains the PMRA's conclusion that there were treatment-related increases in the incidence of uterine adenocarcinomas in female rats at the two highest dose levels in the 24-month chronic toxicity/oncogenicity study with broflanilide.

2. Comments related to the kinetically-derived maximum dose (KMD)

Comment:

The applicant commented that there was a deficiency in reasoning behind the lack of acceptance of the KMD, and that a complete saturation of oral absorption is not a prerequisite to show the occurrence of a saturated absorption system.

PMRA response:

As outlined in the PRD, the applicant initially proposed that the toxicological effects observed in the broflanilide database at dose levels above the KMD were not relevant to humans. It was suggested by the applicant that nonlinear kinetics resulting from saturation of absorption were observed in the database at oral doses greater than approximately 20 mg/kg bw/day in rats. This assertion was based on the results from two types of analyses; the determination of plasma toxicokinetic values (AUC and Cmax) following a single oral gavage dose of radiolabelled broflanilide, and plasma levels of unchanged broflanilide and one metabolite following repeated dietary administration of non-radiolabelled broflanilide.

The KMD is generally determined to be equivalent to, or just slightly above, the dose level representing the inflection point at which toxicokinetic behaviour transitions from linear to nonlinear. Normally, a KMD would be determined before conducting toxicological studies in order to inform dose selection. In the case of broflanilide, the applicant attempted to determine a KMD after many of the toxicity studies had been completed, to support the argument that certain findings noted at high-dose levels were not relevant to human risk assessment, notably the Leydig cell tumours in male rats, as well as ovarian and uterine tumours in female rats.

The PMRA agrees that a change in the absorption rate at higher dose levels was demonstrated by the decreased proportion of radioactive dose absorbed following oral administration of broflanilide with increasing dose level. However, there were a number of issues identified with the applicant's argument, which were outlined in the PRD. This resulted in some uncertainty in supporting the applicant's position regarding the lack of human relevance for effects observed at high-dose levels in studies with broflanilide. Notably, there was a lack of kinetic assessment of compounds other than broflanilide and the metabolite DM-8007 following repeated oral dosing, and a lack of assessment in tissues since only plasma levels were measured. The available data, therefore, may not have provided a reliable indication of the internal dose given that the toxicokinetic data showed that greater levels of radioactivity were observed in tissues when compared to plasma.

In addition to these limitations, the PMRA noted in the PRD that the available data did not demonstrate complete saturation of oral absorption, which the applicant contends does not need to be demonstrated in the determination of a KMD. The PMRA acknowledges that demonstration of nonlinearity in the toxicokinetics of a compound does not rest solely on confirmation of complete saturation of absorption.

In the case of broflanilide, however, the available data do not support the argument that the high-dose toxicity was uniquely associated with saturation of biological processes that control absorption, distribution, metabolism and excretion. There were clear treatment-related dose-responsive toxic effects observed throughout the database, with progression of toxicity and consistent target tissues identified.

Currently, there are ongoing discussions within the international scientific community surrounding the use of KMD in setting dose levels used in toxicity studies and the application of KMD in determining human relevance of toxicological findings. Notwithstanding these discussions, the argument and evidence put forth by the applicant to dismiss several toxicological findings as not being relevant to humans was hampered by certain limitations. In particular, the use of the plasma levels from repeat-dose studies in the evaluation of nonlinearity of toxicokinetics of broflanilide is limited by the fact that the analysis did not account for all breakdown products, with the focus on unchanged broflanilide and one metabolite, nor did it account for tissue concentrations. The limitations in the available data precluded the acceptance of the argument that effects at high-dose levels are not relevant to humans.

Therefore, it remains the PMRA's conclusion that there is insufficient information to support the applicant's argument that the animal toxicity findings observed at high-dose levels in the broflanilide database should be regarded as irrelevant to human health assessment.

3. Comments related to findings in the 2-generation reproductive toxicity study in the rat

Comment:

The applicant commented that the decreased brain, spleen and thymus weights observed in offspring in the 2-generation reproductive toxicity study in rats were secondary to decreased body weight and should not be considered treatment-related.

PMRA response:

In the 2-generation reproductive toxicity study in rats, statistically significant decreases in absolute brain weight were observed at weaning in both sexes of F1 and F2 pups from the two highest dose groups (with the exception of female offspring from the F1 generation for which a decrease in absolute brain weight was only observed at the highest dose tested). These decreases were slight in magnitude (generally less than 5% relative to controls). Offspring body weights at weaning were reduced by 5% to 9% relative to controls at the two highest dose levels tested in the reproductive toxicity study. However, brain weights are usually very stable, and are generally not affected by slight changes in body weight.

Decreases in relative and absolute thymus weights were also observed in F1 and F2 pups from both sexes at the two highest dose levels in the 2-generation reproductive toxicity study. These decreases were statistically significant except for the relative weights in F1 males. Decreases in absolute and relative spleen weights were observed in F1 females, and in absolute spleen weight in F2 males and females, at the highest dose tested.

Decreases in absolute thymus and spleen weights reached magnitudes of up to 23% and 15% relative to controls, respectively, exceeding the magnitude of the body weight decreases. This suggests that the decreased thymus and spleen weights were not solely a result of the altered body weight.

Furthermore, the brain, spleen, and thymus tissues collected from offspring at weaning were not examined microscopically to confirm lack of treatment-related pathology that could be associated with the reduced organ weights. This lack of microscopic examination, combined with the magnitude of the organ weight changes as well as the consistency of the organ weight changes between sexes and between the F1 and F2 generations, led to the PMRA being unable to conclude that the organ weight changes were correlated with the reduced body weights. Therefore, it remains the PMRA's conclusion that the decreases in brain, spleen, and thymus weights in offspring were treatment-related.

Comment:

The applicant commented that increases in absolute and relative testes, cauda epididymis and epididymal weights observed in F1 adult males in the 2-generation reproductive toxicity study should not be considered treatment-related. The applicant noted that there was no histological correlate and that there was a lack of dose-response. The applicant also noted that since these findings should not be considered to be related to treatment, there would be no indication of higher sensitivity of the F1 generation males in comparison to the P generation males.

PMRA response:

The PMRA concluded that there were treatment-related increases in absolute and relative weights of the testes, cauda epididymis and epididymides in F1 generation adult males in the 2-generation reproductive toxicity study. Although there were no correlating histopathological findings, the increased weights were considered to be treatment-related given the magnitude of the findings and the statistical significance with large group sizes (n = 25) associated with the increased weights. The male reproductive system was a target of toxicity in other studies conducted with broflanilide, and toxicokinetics studies revealed that the epididymides were among the tissues to which distribution of broflanilide was evident. It therefore remains the PMRA's conclusion that a relationship to treatment for increases in absolute and relative testes, cauda epididymis and epididymal weights could not be ruled out.

Comment:

The applicant commented that there was no treatment-related effect on the viability index in the 2-generation reproductive toxicity study in rats. The applicant cited the historical control range for this finding and the lack of an effect on lactation index as support for their conclusion.

PMRA response:

The PMRA noted that an increase in the incidence of pup deaths (pups found dead or cannibalized) in the F1 and F2 generations was observed during postnatal days 1–4 at the highest dose tested in the 2-generation reproductive toxicity study. This increase was noted on both a pup and litter basis, with 11 pups in seven litters affected in the F1 generation and six pups in five litters affected in the F2 generation, compared to one pup in one litter in the

control group of each generation. The increased pup deaths early in the post-natal period resulted in a slight reduction in the viability index at the highest dose tested, with indices of 96.3% versus 99.6% in controls for the F1 generation and 98.1% versus 99.7% in controls for the F2 generation. The viability indices for the control groups were comparable to the historical control mean provided by the applicant, although it should be noted that there were some limitations in the historical control data provided. It remains the PMRA's conclusion that the slight decrease in the viability index at the highest dose tested, resulting from the slightly increased number of pups found dead or cannibalized on postnatal days 1–4, was considered to be treatment-related.

4. Comment related to the 90-day study with hormone investigations

Comment:

The applicant commented that the results from the hormonal investigation study in rats suggested that the adrenal gland findings observed throughout the broflanilide database should be considered non-adverse. The applicant noted that the PRD did not include a discussion of the assessment of adrenal gland function investigations that formed part of the 90-day hormonal effects study in rats. The applicant stated that storage of lipids as cholesterol-ester may have resulted in increased adrenal gland weights but did not affect the functional ability of the adrenal gland.

PMRA response:

As indicated in the PRD, the adrenal gland was a target of toxicity throughout the broflanilide database as evidenced by organ weight changes, vacuolation, and hypertrophy. In the non-guideline 90-day study in rats that investigated levels of various hormones after exposure to broflanilide via the diet, a satellite group was included in which cortisone levels were measured before and after being challenged with adrenocorticotropic hormone (ACTH). The PMRA noted that, under the conditions of the study, the results indicated that the adrenal gland of animals exposed to broflanilide appeared to continue to respond to ACTH by producing corticosterone. However, in some instances there was a dose-dependent increase in corticosterone levels observed in certain test groups. Furthermore, the PMRA identified a number of limitations in the non-guideline 90-day study. The corticosterone data from the group without ACTH challenge showed high variability, which rendered it difficult to interpret. For the adrenal gland function tests in satellite animals, a pre-challenge measurement of corticosterone was not taken and no positive control group was included making it difficult to fully interpret the data. Given these limitations, there was a low level of confidence in the non-guideline 90-day study and there remained excessive uncertainty regarding the adrenal gland function and its relation to the broflanilide exposure. It remains the PMRA's conclusion that the treatment-related adrenal gland findings noted throughout the database were toxicologically significant and that an adverse effect on adrenal gland function could not be ruled out.

5. Comment related to findings in the 12-month oral toxicity study in the dog

Comment:

The applicant commented that vacuolation in the adrenal gland in dogs from the 12-month oral toxicity study should not be considered treatment-related. The applicant noted that the presence of vacuolation in the zona fasciculata of the adrenal gland is highly variable in Beagle dogs, and that the increased incidence of this finding was not always consistent with increased adrenal gland weights, enlargement, or hypertrophy of the adrenal cortex.

PMRA response:

In the 12-month oral toxicity study in the dog, there was an increase in macrovesicular vacuolation of the zona fasciculata in males at the mid- and high-dose levels, and in females at all dose levels when compared to controls. The incidences in male and female dogs from the control, low-, mid-, and high-dose levels, respectively, were 2, 2, 3, 3 and 2, 5, 4, 5 out of a total of five animals/sex/group. Historical control data were not provided for this finding. In the same study, an increase in adrenal gland hypertrophy of the cortical cells of the zona fasciculata was observed in males at all dose levels, and in females at the highest dose level. Increased adrenal gland weight and gross enlargement of the adrenal gland were also observed in males at all dose levels and in females at the mid- and high-dose levels. The slightly increased incidence of vacuolation in the adrenal gland was considered treatment-related given the corresponding macroscopic findings and increased adrenal gland weight in the study, and the overall weight of evidence in the database indicating that the adrenal gland was a target of toxicity in rats, mice and dogs. It remains the PMRA's conclusion that the increased incidences of vacuolation in the adrenal gland in this study were treatment-related.

6. Comment related to the proposed mode of action (MOA) for Leydig cell tumours in rats

Comment:

In response to the statement in the PRD that an increase in luteinizing hormone (LH) levels is a key event that is common to various hormone-based MOAs for the formation of Leydig cell tumours and is not specific to the applicant's proposed MOA, the applicant stated that toxicological data and weight of evidence were used to exclude other potential MOAs in regards to the increased LH key event.

PMRA response:

As discussed in the PRD, the applicant submitted a proposed MOA and a human relevance framework analysis for the Leydig cell adenomas observed in male rats in the 24-month chronic toxicity/oncogenicity study with broflanilide. The proposed MOA initially involves a transient decrease in serum testosterone levels followed by increased serum LH levels as the first two key events. In the applicant's presentation of the proposed MOA, alternative known causes of elevated LH levels were discussed and put forth as not being plausible in the case of broflanilide. However, no mechanistic investigations were conducted to exclude these alternative MOAs. As indicated in the PRD, several limitations were noted in the mechanistic study submitted to support the key events of decreased serum testosterone levels followed by increased serum LH levels.

Overall, the presented information to exclude other MOAs related to the increased LH key event was considered to be insufficient, and it remains the PMRA's conclusion that the proposed MOA for the Leydig cell tumours was not adequately supported.

7. Comment related to metabolite toxicity

Comment:

The applicant commented that the characterized metabolites were not of equal toxicity to broflanilide. The applicant noted that no toxic effects were observed with metabolite DM-8007, that effects with metabolite MFBA occurred only at a limit dose, and that metabolites DC-DM and S(PFP-OH)-8007 were of equal toxicity to broflanilide. For metabolites AB-oxa and S(Br-OH)-8007, the applicant noted that acute oral toxicity and genotoxicity studies were provided and that they did not show increased risk for these metabolites, relative to broflanilide.

PMRA response:

The PMRA determined that metabolites DM-8007, DC-DM-8007, S(PFP-OH)-8007, DC-8007, MFBA, AB-oxa, and S(Br-OH)-8007 were to be considered of equal toxicity as broflanilide. This determination was based on the limited toxicity data available for these metabolites, which did not suggest that any of these compounds was of greater toxicity than broflanilide. A definitive conclusion that these metabolites were less toxic than broflanilide, and therefore should not be considered for inclusion in the residue definition for assessing risk from exposure to broflanilide and associated residues, could not be made due to the lack of robust data for comparison. Data for some of these metabolites were limited to acute oral and genotoxicity studies, while for a limited number of metabolites 28-day and 90-day oral toxicity studies were available.

8. Comment related to errors in the PRD

Comment:

The applicant noted a couple of errors in the Toxicology Summary of the PRD. It was noted that there was an error in the data reported for the plasma elimination half-lives, and the incorrect use of the word dermal when reporting the acceptable daily intake (ADI) values.

PMRA response:

The range for the plasma elimination half-life for animals administered the high-dose levels in the toxicokinetic studies was reported in the PRD as 8–58 hours, but should be reported as 10–58 hours. The lower end of the range presented in the PRD of 8 hours represented the elimination half-life from whole blood for female rats administered the high-dose level of the test material radiolabelled on the C-ring of the broflanilide molecule, and was incorrectly included in the summary of plasma elimination data.

It is reported in the PRD that a dermal NOAEL was used to derive the ADI. The word dermal was added by mistake. The NOAEL selected for the ADI value was from the 12-month interim sacrifice group in the 24-month dietary (oral) chronic toxicity/oncogenicity study in the rat.

B. Occupational and residential risk assessment

1. Comment related to dermal absorption

Comment:

The applicant noted that the selection of the overall highest dermal absorption value from the mid-dose group at the earliest sample timing deviates from prior PMRA practice which takes into account variability and continued absorption of residues in the skin at later sacrifice times. Furthermore, PMRA stated, "These results indicate that the dermal absorption values from the groups sacrificed after 8 hours likely overestimate the percent of the dose that will be taken up into the body." As a result, the dermal absorption factor PMRA has set for broflanilide is a highly conservative estimate of potential human dermal absorption.

PMRA response:

A conservative dermal absorption value was chosen based on the limitations in the rat in vivo dermal absorption study related to the number and concentration of the dose levels. Based on the PMRA Science Policy Note on dermal absorption (SPN2016-02), 3–4 doses with concentrations at logarithmic intervals are recommended. However, as the low (1.25 µg/cm^2) and mid-doses (2.5 µg/cm^2) in the study were very similar in concentration (in other words, not logarithmic), the study was considered to be representative of only two dose levels (mid- and high-doses). As such, the study was not considered to have met the criteria for the number of doses. For dermal absorption studies without such design limitations, the continued absorption of residues in the skin at later sacrifice times is taken into consideration when establishing a dermal absorption value.

2. Comment related to occupational exposure and risk

Comment:

The applicant noted that for the occupational seed treatment risk assessment reported in this PRD, PMRA has changed their policy on the source of the unit exposures used for seed treatment worker risk assessment, which has changed some of the scenarios evaluated, the unit exposure values relied upon, and the default personal protective equipment (PPE) worn by workers in the represented studies. Previous seed treatment risk assessments relied on registrant submitted studies which were evaluated by PMRA, the details of which were included in the risk assessment. This allowed registrants to have a clear understanding of the inputs used by PMRA and allowed replication of the risk assessments. It would benefit registrants if PMRA would publicly announce the change in their seed treatment risk assessment policy, including a detailed review of the studies relied upon, before a new policy is implemented. This would increase transparency of the risk assessment process and enable registrants to conduct risk assessments for new uses following PMRA practice before a new use is submitted.

PMRA response:

The studies chosen by the PMRA to conduct the occupational seed treatment risk assessment are owned by the Agricultural Handlers Exposure Task Force (AHETF), of which BASF is a member. As such, BASF has access to the studies and the unit exposure values used to complete all the risk assessments for broflanilide. The studies chosen have previously been used by the PMRA to register seed treatment products and there has been no change in the PMRA seed treatment risk assessment policy.

The PMRA deviated from the worker exposure studies recommended by BASF because they were not considered acceptable surrogates for cereals based on the dust-off data provided by BASF. The dust-off data demonstrated that wheat seed is approximately two times dustier than corn seed, therefore, worker exposure studies conducted with corn could not be used to represent worker exposure to treated wheat. Also, the BASF referenced studies did not account for on-farm treatment and planting, thus a study had to be sourced from the PMRA database of AHETF studies.

The PMRA chose studies which were the most relevant to the proposed use pattern of Terexxa and Terexxa F4 based on the following parameters: treatment system (open vs closed), monitoring duration, application rate, amount of active ingredient handled per day, number of seeds or hectares planted per day and seed packaging.

3. Comments related to mixer/loader/applicator exposure and risk assessment

Comment:

The applicant noted that the language on the draft proposed labels was carried over from a previous seed treatment label. It was not based on preliminary risk assessment for broflanilide. In addition, the unit exposures used for workers in commercial facilities (including mobile treaters) was based on dosimetry studies where workers wore a single layer of clothing and chemical resistant gloves, but they did not wear coveralls. The risk assessment for broflanilide using these unit exposures was acceptable without coveralls. Therefore, if specific PPE is not required to reduce handler exposure, it should not be required on the label.

PMRA response:

The PMRA does not remove PPE from a label proposed by the applicant. However, as noted in the comment, BASF supports the removal of the PPE as it was carried over from a previous seed treatment label and is not required to reduce handler exposure. In addition, the risk assessment also does not warrant this PPE. As such, the PMRA can support the removal of coveralls for commercial and mobile treaters for Teraxxa only. The presence of additional active ingredients in Teraxxa F4 necessitates that coveralls remain on the label as they are present on the registered precedent product labels.

Comment:

The applicant noted that the language on the draft proposed labels was carried over from a previous seed treatment label. It was not based on preliminary risk assessment for broflanilide. In addition, the unit exposures used for workers bagging/sewing/stacking in commercial facilities was based on dosimetry studies where workers wore a single layer of

clothing and no gloves, and they did not wear coveralls. The risk assessment for broflanilide using these unit exposures was acceptable without coveralls. Therefore, if specific PPE is not required to reduce handler exposure, it should not be required on the label.

PMRA response:

The PMRA does not remove PPE from a label proposed by the applicant. However, as noted in the comment, BASF supports the removal of the PPE as it was carried over from a previous seed treatment label and is not required to reduce handler exposure. In addition, the risk assessment also does not warrant this PPE. As such, the PMRA can support the removal of coveralls for workers bagging/sewing/stacking treated seed for Teraxxa only. The presence of additional active ingredients in Teraxxa F4 necessitates that coveralls remain on the label as they are present on the registered precedent product labels.

Comment:

The Applicant agrees that the higher exposures encountered by workers cleaning seed treatment equipment warrants requiring them to wear chemical-resistant coveralls and chemical-resistant gloves as worn by workers in the surrogate study used to derive the unit exposures for this activity

PMRA response:

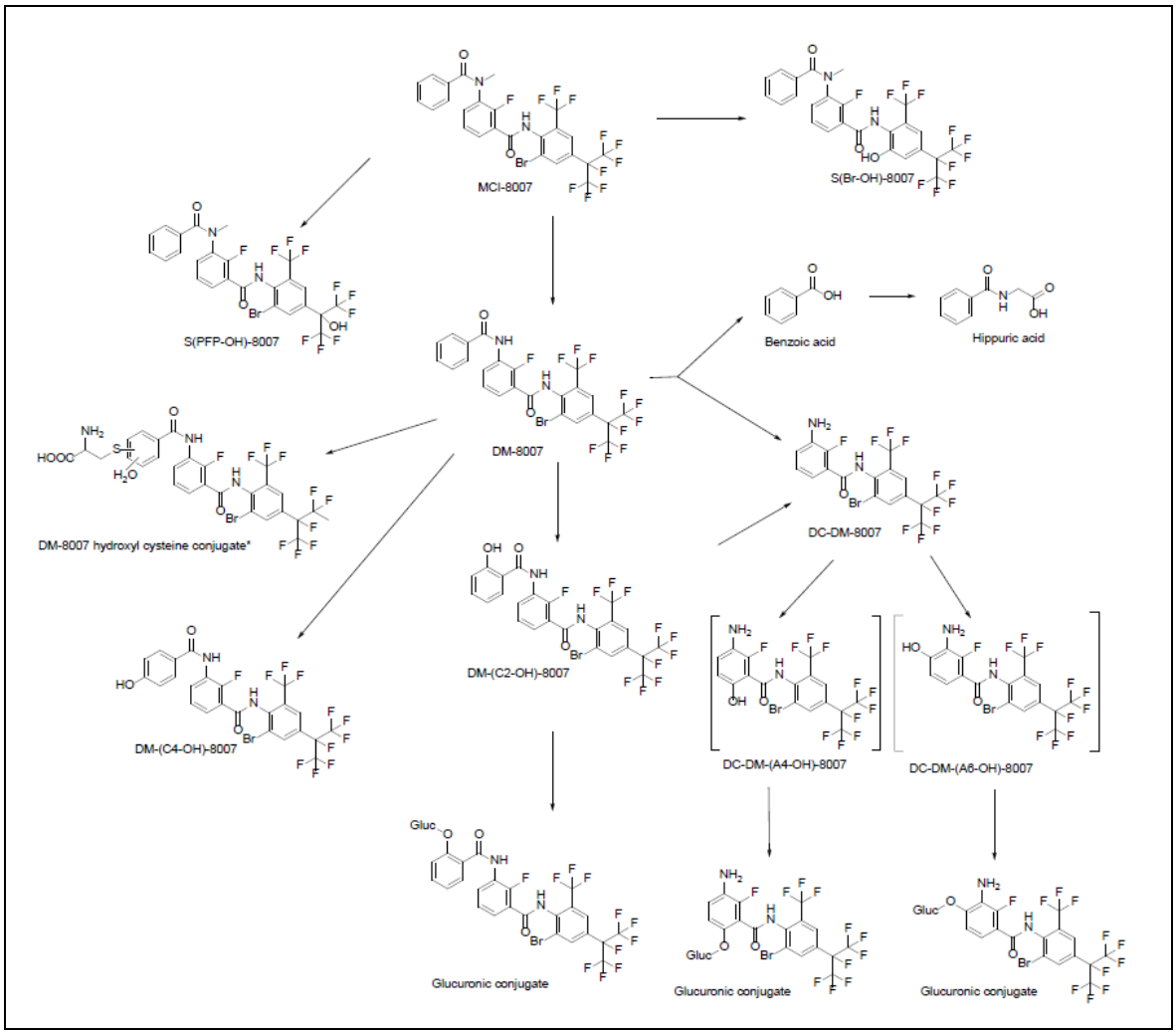
No further comments.

C. Food residues exposure assessment

1. Comments to Appendix I, Table 12 integrated food residue chemistry summary

Comment:

The Applicant commented on the Nature of Residue in the Lactating Goat – Proposed Metabolic Scheme in Livestock on page 70. The Applicant stated that for a comprehensive assessment of the metabolic pathway in livestock, the overall pathway covering hen and goats is considered as more appropriate. The Applicant would kindly ask to replace it with the following:



PMRA response:

PMRA has no objection with replacing the metabolic pathway in the PRD2020-06 with the above enclosed in the comment.

Comment:

The Applicant commented on the Nature of Residue in Tomato, page 75, TRR columns. The Applicant stated that the metabolism in tomatoes follow the same degradation pathway as observed in all other crops. Hydroxylation and desmethylation are the only metabolic conversions observed; no cleavage between the ring systems was found. Due to a transposition error, misleading conclusions might be drawn from the document. For this reason, the Applicant asks PMRA to correct the entries in the table as follows:

Matrices	PHI (days)	[14C-C-ring] TRR [ppm]
Leaves	71 (71DAT1)	<0.001
Leaves Surface Rinse		0.000
Rinsed Leaves		0.000

Fruits		<0.001
Fruit Surface Rinse		Non detectable
Rinsed Fruits		Non detectable
Leaves	10 (10DAT2)	0.851
Leaves Surface Rinse		0.678
Rinsed Leaves		0.226
Fruits		0.01
Fruit Surface Rinse		0.008
Rinsed Fruits		0.002

Matrices	PHI (days)	[14C-B-ring] TRR [ppm]
Leaves	10 (10DAT2)	1.596
Leaves Surface Rinse		1.057
Rinsed Leaves		0.539
Fruits		0.01
Fruit Surface Rinse		0.007
Rinsed Fruits		0.003

PMRA response:

PMRA acknowledges the transcription error and recommends the following revisions to the table of tomato TRRs currently in the PRD2020-06.

Matrices	**PHI (days)**	**[^{14}C-B-ring] TRR (ppm)**	**[^{14}C-C-ring] TRR (ppm)**
Leaves	71 (71DAT1)	≤0.001	≤0.001
Leaves Surface Rinse		0.000	0.000
Rinsed Leaves		0.001	0.000
Fruits		≤0.001	≤0.001
Fruit Surface Rinse		Not detectable	Not detectable
Rinsed Fruits		Not detectable	Not detectable
Leaves	10 (10DAT2)	1.596	0.851
Leaves Surface Rinse		1.057	0.678
Rinsed Leaves		0.539	0.226
Fruits		0.01	0.01
Fruit Surface Rinse		0.007	0.008
Rinsed Fruits		0.003	0.002

2. Comment to Maximum Residue Limits (table 3.6.1 and section 7.1)

Comment:

In Canada, the crops intended by the Applicant include corn (all types) and the following small cereal grains: barley, buckwheat, pearl millet, proso millet, oats, rye, sorghum, triticale, canary seed, annual canarygrass (grown for human consumption), wheat (all types: winter, spring and durum). The Canadian Applicant did not request as labelled crops some of the small cereal grains which the U.S. Applicant requested since the applicant did not have the required crop tolerance data for these crops (i.e., amaranth grain, cañihua grain, chia grain, cram-cram grain, huauzontle grain, quinoa, spelt grain, teff grain). These additional small cereal grains fall outside of CG 15. The applicant proposed a revised table 3.6.1 (below). New proposed text is shown in bold. Proposed MRLs for these crops are to allow importation from the U.S.

In addition, the Applicant has modified "Food commodities (other than those listed in this item)" to reflect that the proposed MRL of 0.01 ppm allows for importation from the United States of food commodities which were exposed to the insecticide during treatment of food-handling establishments where food and food products are held, processed, prepared, or served.

Table 3.6.1 Proposed Maximum Residue Limits (also applies to table under Section 7.1, p. 42)

Commodity	**Recommended MRL (ppm)**
Tuberous and corm vegetables (CSG 1C)	0.04
Eggs, fat, meat, and meat byproducts of cattle, goats, hogs, horses, sheep and poultry, milk	0.02
Cereal grains (CG 15), except rice	0.01
Annual canarygrass seeds	**0.01**
Other small cereal grains (amaranth grain, cañihua grain, chiagrain, cram-cram grain, huauzontle grain, quinoa, spelt grain, teffgrain)	0.01[1]
All food commodities (other than those already covered by a higher MRL as a result of use on growing crops) in food-handling establishments where food products are held, processed or prepared	0.01[1]

[1] The uses are not on the Canadian label. Proposed MRLs are to allow importation from the United States.

PMRA response:

The PMRA acknowledges that the American Applicant requested the registration of several small cereal grains that are not part of the current crop group 15. Therefore, to allow the importation of these cereal grains into Canada, the PMRA is proposing to set MRLs for these

cereal grains at the same level as those grains on the Canadian registered label. For this reason, all cereal grains were listed together. In the Broflanilide PMRL and the WTO Notification, no distinction is made between registered cereal grains and those imported from the United States. This distinction is also not made in the MRL Database for currently established MRLs. Nevertheless, to provide further clarity to the proposed MRLs in the PRD, the MRL tables will be revised as noted below to list wild rice as one of the cereal grain exceptions and to clearly highlight which cereal grain MRLs are proposed to allow for importation.

For the proposed MRL recommended to allow importation from the United States of food commodities which were exposed to the treatment of food-handling establishments, the descriptor in the PRD, PMRL and WTO Notifications is consistent with that for current MRLs (iprodione, phoate, methomyl). Furthermore, stakeholders relying on the MRL database (in other words,, growers, importers, exporters) may not be able to distinguish which MRL applies to a growing crop or not. Further to this, the descriptor proposed by PMRA allows flexibility in the event that, in the future, new MRLs are specified for other crops at the same level (0.01 ppm), either as a result of registration or importation. Thus, the descriptor must remain as proposed in the PRD, with a minor revision as noted below.

PMRA REVISED Table 3.6.1 Proposed Maximum Residue Limits (also applies to table under Section 7.1, p. 42)

Commodity	Recommended MRL (ppm)
Tuberous and corm vegetables (CSG 1C)	0.04
Eggs, fat, meat, and meat byproducts of cattle, goats, hogs, horses, sheep and poultry, milk	0.02
Cereal grains (CG 15, except rice and wild rice), annual canarygrass seeds	0.01
Amaranth grain, cañihua grain, chiagrain, cram-cram grain, huauzontle grain, quinoa, spelt grain, teffgrain	0.01[1]
All food crops (other than those listed in this item)	0.01[1]

[1] The uses are not on the Canadian label. Proposed MRLs are to allow importation from the U.S.

D. Environmental assessment

1. Comment relating to the residue definition used in kinetic evaluations

Comment:

The Applicant questioned whether unextracted residues were included in the Illinois processed soil aerobic biotransformation kinetic evaluations.

PMRA response:

Unextracted residues were not included in the Illinois processed soil aerobic biotransformation kinetic evaluation. Parent-only residues were considered in all kinetic calculations.

2. Comment relating to the length of the datasets used in the aerobic soil biotransformation kinetic evaluations

Comment:

The Applicant asked for confirmation of whether truncated 120-day datasets (considering parent-only residues) were used for the Tennessee and North Carolina soils, and whether a 365-day dataset (considering parent-only residues) was used for the California soil.

PMRA response:

The truncated 120-day datasets (parent-only residues) were used for the Tennessee, North Carolina, and Illinois aerobic soil biotransformation kinetic evaluations, as soil microbial biomass was determined to be unacceptably low at 365 days. In the separate California study, the 365-day dataset (parent-only residues) was used in kinetic evaluation, as the reported reduction in soil microbial biomass over the course of the 365-day study was not considered to have impacted biotransformation processes.

3. Comment relating to the use of mean-measured concentrations in aquatic endpoint determination

Comment:

The Applicant questioned the use of mean-measured concentrations in aquatic endpoint determination, in cases where measured concentrations remained within 20% of nominal during the study.

PMRA response:

Many aquatic endpoints were expressed as mean-measured concentrations instead of nominal; however, many of these re-calculations were minor, with little impact on the risk assessment.

It is not standard practice for the PMRA to express endpoints as mean-measured concentrations, in cases where measured concentrations remain within 20% of nominal during a study. These re-calculations were conducted by the USEPA and were considered acceptable by the PMRA at the time of review of broflanilide. This was done in an effort to have harmonized endpoints for the joint review.

4. Comment relating to the endpoint determination for the seedling emergence terrestrial vascular plant study.

Comment:

The Applicant questioned the endpoint determination for cabbage and sugarbeet in the 21-day seedling emergence terrestrial vascular plant study, as it was suggested that there was no evidence for dose-dependent effect, and that there was poor fit of the non-linear regression to the empirical data.

PMRA Response:

The PMRA is in agreement that the observed effects on sugarbeet and cabbage survival in the 21-day seedling emergence study did not manifest in a dose-responsive manner, and regression-based toxicity endpoints (EC_{25} values) were highly uncertain. However, this study is designed to capture sub-lethal effects; therefore, survival is not expected to be the most sensitive endpoint, and may impact the validity of the other endpoints measured in the study. It is noted that similar effects were also observed in the Tier I portion of the seedling emergence study.

The use of these conservative endpoints in the screening level risk assessment is considered appropriate. Regardless of the conservative endpoint selection, the use of broflanilide is not expected to pose a risk to non-target terrestrial vascular plants. No mitigative measures are required for the protection of terrestrial plants from the use of broflanilide.

5. Comment relating to the endpoint determination for the honey bee larval chronic study

Comment:

The Applicant questioned the endpoint determination in the 22-day honey bee larval chronic study. It was indicated that the PMRA use of a NOAEL based on 8-day larval mortality was not appropriate, as the study is designed to calculate an endpoint based on 22-day adult emergence data, and that the larval mortality observed in this study could be an artefact of handling of the sensitive larval stage. It was further remarked that dividing the NOAEL by a factor of 4 in order to convert the cumulative dose (larvae are repeatedly fed over 4 days) into a per-day dose basis was not appropriate as the provisioned diet is not entirely consumed within the 24-hour period. Rather, the majority of diet is consumed during the last couple of days.

PMRA response:

Larval mortality averaged 8 and 11% in the negative and solvent controls, respectively, as compared to larval mortality ranging from 6–47% in the exposed groups, in a dose-responsive manner. The dose-responsive larval mortality observed in this study cannot be attributed to handling of the larvae, and cannot be precluded from the assessment of chronic risk to honeybee larvae.

The expression of the NOAEL on the basis of ng/larva/day is used to correlate toxicity endpoints derived in the laboratory studies to estimated environmental concentrations based on consumption rates, and is a harmonized approach with the USEPA as outlined in the Guidance for Assessing Risks to Bees (USEPA, HC-PMRA, CDPR, 2014).