Proposed Special Review Decision PSRD2019-01

Special Review for Bromoxynil and Its Associated End-use Products

Consultation Document

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1.0 Introduction

Pursuant to subsection 17(2) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) has initiated a special review of 3,5-dibromo-4-hydroxybenzonitrile (Canada, 2013), hereafter referred to as bromoxynil. This special review was based on the decision taken by Norway in 2000 to prohibit the use of bromoxynil octanoate (CAS No. 1689-99-2) due to human health and environmental concerns (Rotterdam Convention, 2001).

Pursuant to subsection 18(4) of the *Pest Control Products Act*, the PMRA has evaluated the aspects of concern that prompted the special review of pest control products containing bromoxynil. The aspects of concern for this special review are relevant to human health and the environment.

2.0 Uses of Bromoxynil in Canada

Bromoxynil is an herbicide registered in Canada for commercial use to control a wide spectrum of annual broadleaf weeds in food and feed crops including alfalfa, corn, wheat, onions, garlic, carrots, and several seedling grasses. In currently registered products, bromoxynil is present as bromoxynil octanoate, bromoxynil heptanoate, and bromoxynil phenol, and all currently registered products containing the above forms (Appendix I) are considered in this special review.

3.0 Aspects of the Pest Control Product that Prompted the Special Review

Based on the review of the Norwegian decision (Rotterdam Convention, 2001), the PMRA identified the aspects of concern that prompted the special review of bromoxynil as:

Human Health

- Potential carcinogenicity;
- Potential developmental effects;
- Potential occupational risk (mixer, loader, and applicator)

Environment

- Potential risk to aquatic organisms

4.0 Evaluation of the Aspects of Concern that Prompted the Special Review

Following the initiation of the special review of bromoxynil, the PMRA requested information from provinces and other relevant federal departments and agencies in accordance with subsection 18(2) of the *Pest Control Products Act*. In response, water monitoring data was received and was considered in the special review.

In order to evaluate the aspects of concern, the PMRA has considered all currently available relevant scientific information, which includes information submitted by registrants as part of the special review, existing reviews (Canada, 2008a; Canada, 2008b), and any relevant information obtained since 2008 (for example, available monitoring data, incident reports, Norwegian decision, and relevant information published by the European Union (European Commission, 2016) and the United States Environmental Protection Agency (USEPA) (United States, 2012; United States, 2013)).

4.1 Potential Carcinogenicity

As part of the special review, the PMRA re-assessed the potential carcinogenicity of bromoxynil based on the currently available information.

In a study in Sprague Dawley rats, the liver was identified as a target organ but no treatment-related tumours were apparent at doses up to 28 mg/kg bw/day (males) or 41 mg/kg bw/day (females).

Two long-term dietary studies with bromoxynil phenol in mice were available: one conducted in Swiss mice and one conducted with higher doses in CD-1 mice. In the Swiss mouse study (1, 4 and 13 mg/kg bw/day), the combined incidence of hepatic adenomas and carcinomas in males increased in a dose-related manner. No treatment-related increased incidence of tumours was seen in female Swiss mice. In the CD-1 mouse, the combined incidence of hepatic adenomas and carcinomas in males was increased relative to control animals at every dose level tested (3, 12 and 46 mg/kg bw/day) but the dose response was not linear. An increased incidence of hepatic adenomas and carcinomas (combined) was also noted in female CD-1 mice at 53 mg/kg bw/day.

Information submitted by the registrant as part of the special review proposed a mode of action (MOA) to address the observed hepatic adenomas and carcinomas. The MOA focused on the generation of hepatocellular tumours through the activation of peroxisome proliferator-activated receptor alpha (PPARα), leading to alterations in cell growth pathways, subsequent perturbation of cell growth and survival, then selective clonal expansion of pre-neoplastic cells, and ultimately, the production of hepatic tumours.

Overall, the key events for the bromoxynil liver tumours were clear and demonstrable to support a receptor-mediated cell proliferative MOA. The strongest evidence was for a PPARα-mediated process, but the PMRA found that the influence of constitutive androstane receptor (CAR) activity could not be excluded. The dose and temporal concordance were generally acceptable for the parameters that were observed; however, there was a lack of information available to describe the onset of PPARα activation and the subsequent alteration of cell growth pathways at non-tumorigenic dose levels. Despite this shortcoming, the key events were consistently observed throughout the database and were in accordance with liver effects anticipated in a receptor-mediated cell proliferative pathway. The proposed MOA was considered biologically plausible and coherent.

However, as the role of PPARα activity could not be clearly differentiated from that of CAR, it was determined that human relevance could not be discounted on the basis of the available data. It was determined that use of a q1* for risk assessment was overly conservative given the data, and that the tumors (regardless of whether PPAR or CAR-mediated) could be addressed through a threshold approach.

The acceptable daily intake (ADI) of 0.003 mg/kg bw/day, based on a no observed adverse effect level (NOAEL) of 0.3 mg/kg bw/day, provided a margin of 1000 to the lowest tumorigenic dose of 3 mg/kg bw/day, and it is considered protective of potential carcinogenicity. Concern for potential carcinogenicity following short/intermediate-term dermal and inhalation exposures can be allayed based on the etiology of the receptor-mediated cell proliferative MOA, as tumour induction via this MOA requires a sustained proliferative response. No evidence of cell proliferation was observed in short- to intermediate-term mouse studies in the database at dose levels similar to those used for the points of departure for dermal (10 mg/kg bw/day) and inhalation (5 mg/kg bw/day) reference values. Accordingly, the dermal, and inhalation reference values are protective for any potential carcinogenicity concerns.

Overall conclusion regarding the potential carcinogenicity of bromoxynil: The PMRA review of the available toxicological database for bromoxynil determined, that bromoxynil is not mutagenic or genotoxic based on the collective data from several in vitro and in vivo tests. Bromoxynil was found to be carcinogenic in mice but not in rats. The weight-of-evidence supported a proposed receptor-mediated cell proliferative MOA for the observed bromoxynil-induced hepatocarcinogenesis in mice, and a threshold approach was deemed appropriate for characterization of potential cancer risks in humans. The reference values selected for characterization of non-cancer risks resulting from repeated exposure to bromoxynil (Appendix II) are protective of any residual concerns regarding the oncogenic potential of bromoxynil. On this basis, a separate cancer risk assessment is not required.

4.2 Potential Developmental Effects

The PMRA reviewed the available toxicological database for bromoxynil as well as information available in the public domain (European Commission, 2016; United States, 2012) to assess potential developmental effects of bromoxynil. Developmental toxicity was evident in the database for bromoxynil phenol and bromoxynil octanoate. In rodents, the developmental effect that was most consistently observed was an increased incidence of the skeletal variation, supernumerary rib (14th rib). The rat was the most sensitive species for developmental toxicity associated with bromoxynil phenol and its octanoate form. Supernumerary ribs were the most sensitive endpoint in oral and dermal developmental toxicity studies and were considered as the point of departure for developmental toxicity. In oral studies, this effect was observed as low as 12 mg/kg bw/day (bromoxynil phenol) and 22 mg/kg bw/day (bromoxynil octanoate). In dermal developmental toxicity studies, supernumerary ribs were noted at 50 mg/kg bw/day and 15 mg/kg bw/day (bromoxynil phenol and bromoxynil octanoate, respectively). Fetal malformations were seen at higher dose levels; microphthalmia was the most consistent observation.

Additional developmental effects included fusion of ribs or other skeletal structures, incomplete ossification in various areas, anophthalmia and decreases in fetal body weights. Fetal effects in rodents always occurred in the presence of maternal toxicity, which ranged from decreases in body weight and body weight gain and increased liver weights, to mortality.

In rabbits, fetal effects occurred at doses lower than those causing toxicity in maternal animals. Decreased fetal body weight, an increased incidence of supernumerary ribs and, at higher doses, malformations including microphthalmia, were repeatedly observed in oral studies with bromoxynil. At higher dose levels, mortality and abortions occurred in the dams. The lowest effect level for developmental toxicity was 15 mg/kg bw/day and was based on decreased fetal body weight and an increased incidence of supernumerary ribs. Malformations were observed at 150 mg/kg bw/day in a dermal bromoxynil phenol study; the establishment of a maternal NOAEL was precluded by dosing errors. No developmental toxicity was observed up to 80 mg/kg bw/day in a dermal study conducted with a formulation containing bromoxynil octanoate.

Overall conclusion regarding potential developmental effects of bromoxynil*:* Bromoxnil exposure results in developmental toxicity in animal studies. The observed increase in the incidence of supernumerary ribs in rats was considered the most sensitive endpoint of developmental toxicity. This effect was not considered a serious endpoint and occurred in the presence of maternal toxicity. Reference values were established taking into account the potential for developmental toxicity (see Appendix II, Table 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. This factor takes into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and post-natal 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, pre-natal developmental toxicity studies in mice, rats and rabbits, a multi-generation reproduction study in rats, as well as supplemental developmental toxicity studies, were available.

No sensitivity of the young animal was noted in the reproduction study. Effects in the offspring, namely bodyweight reductions and delayed eye opening, were observed at the same level that produced bodyweight reductions in adult animals. With respect to potential pre-natal toxicity, developmental effects occurred in the presence of maternal toxicity in rats and mice. Developmental effects at the lowest doses were limited to variations (increased incidence of supernumerary ribs) or decreased fetal body weight; neither of these effects was considered a serious endpoint. Malformations, considered serious endpoints, occurred at higher doses. In rabbits, developmental effects occurred below doses resulting in maternal toxicity; these effects included variations, malformations and reduced fetal weight/size.

The increase in the incidence of supernumerary ribs in rats was considered the most sensitive endpoint of developmental toxicity. It was not considered a serious endpoint and it occurred in the presence of maternal toxicity. In consideration of this, the *Pest Control Products Act* factor

(PCPA factor) was reduced to onefold when this endpoint was selected for risk assessment. Selection of this endpoint and the accompanying PCPA factor provides adequate margins to the malformations; it is also protective of the identified sensitivity of the rabbit fetus. For risk assessments not employing the developmental toxicity endpoint, the PCPA factor was also reduced to onefold as the selected endpoints and uncertainty factors were protective of developmental toxicity.

4.3 Characterization of the Potential Human Health Risks of Bromoxynil

To determine if risk to Canadians from exposure to bromoxynil was acceptable, the PMRA conducted scientifically-based risk assessments relative to the aspects of concern. Toxicology reference values considered for the risk assessments are outlined in Appendix II.

When assessing health risks, the PMRA considers two key factors – the levels at which no adverse health effects occur, and the levels to which people may be exposed. The levels used to assess risks are established to protect the most sensitive human population, for example, children and nursing mothers. As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below the levels that cause no effects in animal testing are considered acceptable for registration.

Exposure to bromoxynil may occur through consuming food and drinking water, working as a mixer/loader/applicator, and/or by entering treated sites to perform postapplication activities. Residential exposure to spray drift may also occur. As such, the PMRA assessed potential non-occupational (Section 4.3.1 to 4.3.3) and occupational (Section 4.4) risks resulting from exposure to bromoxynil.

4.3.1 Dietary Exposure and Risk Assessment: Aggregate dietary risk assessment incorporates exposure from food and drinking water and the toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose and is of concern when the estimated dietary risk exceeds 100% of the reference dose. The acute (ARfD) and chronic (ADI) reference doses for bromoxynil are summarized in Appendix II.

For the purpose of the dietary risk assessment, the Canadian residue definition of bromoxynil in plants (except canola) and animals is bromoxynil. The residue definition in canola is bromoxynil plus the metabolite 3,5-dibromo-4-hydroxybenzoic acid (DBHA). The residue definition in water is bromoxynil plus DBHA. Parent and transformation products were considered to be equivalent in toxicity.

Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02) program which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2005-2010, available through Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS).

The basic acute and chronic dietary assessments were performed using Canadian Maximum Residue Limits (MRLs), American tolerances for imported commodities, and default processing factors. Refinements included the use of the highest (acute) and median (chronic) field trial residues, experimental processing factors (where available), and anticipated residues in animal commodities.

Estimated environmental concentrations (EECs) for the combined residue of bromoxynil and its transformation product DBHA in potential sources of drinking water were modelled using the Surface Water Concentration Calculator (SWCC) model on a standard Level 1 scenario (a small reservoir). EECs in groundwater were calculated using the Pesticide Root Zone Model Groundwater (PRZM GW). The following Level 1 EECs were used for the drinking water input values:

- EECs for use in acute dietary exposure estimates: 32 µg a.e./L; and
- EECs for use in chronic dietary estimates: 4.7 µg a.e./L.

In addition to modelling, available groundwater and surface water monitoring data were considered by the PMRA. There were no quantifiable detections of bromoxynil in Canadian groundwater sources. Bromoxynil has been detected in surface water in the provinces of Alberta, Manitoba, Saskatchewan, Ontario, and Quebec. The Canadian data shows that the overall detection frequency is less than 50% in most studies, with maximum single concentrations in potential surface water sources of drinking water being less than or equal to 0.96 µg/L. The currently available data does not allow for a representative long term exposure value to be determined based on the monitoring information. Thus, the modelled screening level EECs were used in the dietary risk assessment for bromoxynil and are considered conservative as they are approximately 32 (acute) and 4.5 (chronic) times higher than the maximum level of bromoxynil detected in Canadian drinking water sources.

The refined acute aggregate (food plus drinking water) dietary exposure to bromoxynil and its transformation product (DBHA) at the 95th percentile is 3% of ARfD for the general population, and it ranges from 2% to 8% of the ARfD for all subpopulations (8% of the ARfD for all infants, and 4% of the ARfD for females 13-49 years old).

The refined chronic aggregate (food plus drinking water) dietary exposure to bromoxynil and its transformation product (DBHA) is 15% for the general population, and it ranges from 10% to 59% of the ADI for all subpopulations (59% of the ADI for children 1-2 years old, and, <30% of the ADI for all infants).

Based on the results of the dietary exposure assessment, the PMRA concluded that both acute and chronic dietary risks from exposure to residues of bromoxynil are considered to be acceptable for all populations under the current conditions of use. No further risk mitigation measures are proposed.

4.3.2 Residential (Non-Occupational) Exposure and Risk Assessment: There are no registered domestic-class products containing bromoxynil; therefore, domestic handler exposure is not anticipated. Further, commercial-class products are not registered for use in residential

areas. As such, dermal and inhalation exposure to individuals from handling bromoxynil or entering a treated area at home are not expected. Nonetheless, there is a potential for bystander inhalation exposure to spray drift that results from agricultural applications of bromoxynil.

Current labels have statements to mitigate spray drift to residential areas, and potential bystander exposure to spray drift is considered to be significantly lower than the inhalation exposure of an applicator, for whom the potential inhalation risks are considered to be acceptable under current conditions of use (see Section 4.4 for further details). On this basis, the PMRA concluded that the potential residential risk is considered to be acceptable for all populations under the current conditions of use. No further risk mitigation measures are proposed.

To meet the current labelling standard and for consistency, updates to standard spray drift statements are proposed to be included on current labels (Appendix V).

4.3.3 Aggregate Assessment: Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources from all known or plausible exposure routes (oral, dermal, and inhalation). For bromoxynil, aggregate exposure is limited to food and drinking water only, as the potential bystander inhalation exposure is expected to be negligible and is not considered to significantly contribute to the overall exposure to bromoxynil. As described in Section 4.3.1, aggregate dietary exposure to bromoxynil residues from food and drinking water is considered to be acceptable for all population subgroups. No further risk mitigation measures are proposed.

4.3.4 Cumulative Assessment: The *Pest Control Products Act* requires that the PMRA consider the cumulative effects of pest control products that have a common mechanism of toxicity. For the current special review, the PMRA did not identify information indicating that bromoxynil shares a common mechanism of toxicity with other pest control products. Therefore, there is no requirement for a cumulative risk assessment at this time.

4.3.5 Overall Conclusion on Potential Non-Occupational Risks: Based on the risk assessments, potential risks resulting from non-occupational exposure to bromoxynil residues are considered to be acceptable for all populations under the current conditions of use. No additional mitigation measures are proposed.

4.4 Characterization of the Potential Occupational Health Risks

Occupational risk is estimated by comparing potential exposure with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This value is then compared to a target MOE which incorporates uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Mixer/Loader/Applicator Exposure and Risk: Based on the current bromoxynil use pattern, mixer/loader/applicator (M/L/A) exposure is expected to be short-to-intermediate term and to occur via both dermal and inhalation exposure routes.

Daily exposures to workers mixing, loading, and applying bromoxynil using groundboom and aerial application equipment were estimated using exposure data from the Pesticide Handlers Exposure Database (PHED) and/or the Agricultural Handlers Exposure Task Force (AHETF). Standard assumptions included default area treated per day (ATPD) values, maximum application rates as per current labels, and an average worker body weight of 80 kg. Since the dermal reference dose for bromoxynil was based on a dermal study, a dermal absorption value was not required for the assessment. The inhalation reference dose was based on an oral study, and an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation. The assessment considered the minimum PPE as specified on some current bromoxynil product labels, as well as additional PPE when risks of concern were identified for workers under current conditions of use.

Based on the results of the risk assessment (Appendix III, Table 1), the PMRA determined that potential short- to intermediate-term combined (dermal + inhalation) risk for mixers/loaders/applicators using groundboom application equipment is considered to be acceptable with the use of the following additional PPE:

- Mixers/Loaders: coveralls, a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks during mixing, loading, clean-up and repair; and

- Applicators: a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks during open-cab groundboom. Chemical-resistant gloves are not required for closed-cab groundboom application.

Certain product labels do not include the above PPE requirements. Therefore, for consistency and to improve clarity, updates to the PPE requirements are proposed.

For the aerial application scenario, the risk to aerial mixers/loaders and applicators is considered to be acceptable under current conditions of use. No additional mitigation measures are required.

Postapplication Exposure and Risk: Bromoxynil is regarded as non-volatile with a vapour pressure of 1.425×10^{-6} mm Hg at 25°C (Canada, 2008a). The volatility of this active ingredient is below the NAFTA criterion for a waiver of inhalation exposure data for outdoor uses (vapour pressure of less than 7.5×10^{-4} mm Hg; NAFTA, 1999) and, assuming at least 12 hours have passed before re-entry, inhalation exposure to bromoxynil is not expected for postapplication workers re-entering treated sites. Thus, dermal exposure is considered to be the primary route of exposure for workers entering treated fields to conduct postapplication activities, and it is expected to be short-to-intermediate term in duration.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before workers can enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse in order to allow residues to decline to a level where there are no risks of concern for postapplication worker activities. Current end-use product labels specify a 24-hour REI for all uses.

Dermal exposures on the day of application (day 0) for workers entering treated sites to perform postapplication activities were estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residues (DFRs). A transfer coefficient (TC), usually expressed in units of cm^2 per hour, expresses the relationship between worker dermal exposure and dislodgeable residues found on bromoxynil-treated plants. Transfer coefficients are specific to a given crop (and crop stage) and activity combination, and they reflect standard agricultural work clothing worn by postapplication adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used in the risk assessment. In the absence of chemical-specific DFRs, default DFRs were calculated assuming a 25% deposition of bromoxynil residues following application at the maximum application rate and a10% dissipation rate of these residues per day. Additional assumptions used included an 8 hour workday and an average worker body weight of 80 kg. For crops with two applications at the maximum rate, a re-treatment interval of 10 days for onion (as per current label directions) or 21 days for sweet corn and established alfalfa (based on current use practices) was assumed. Since the dermal reference dose for bromoxynil was based on a dermal study (Appendix II), a dermal absorption value was not required for the assessment.

The dermal risk assessment for workers performing postapplication activities in outdoor crops is presented in Table 2 of Appendix III. The target dermal MOE of 100 was met or exceeded for all applicable crops/activities at the 24-hour REI specified on the current labels with the exception of handset irrigation (sweet corn and garlic) and hand harvesting (sweet corn). Consequently, the following REIs are proposed to be included on the current end-use products labels:

- Sweet corn, handset irrigation – 5 day REI;
- Sweet corn, hand harvesting – 20 day REI; and
- Garlic, handset irrigation – 2 day REI.

4.4.1 Overall Conclusion for Occupational Risks

Based on the occupational risk assessments, the PMRA has concluded that:

- Potential risk to workers mixing/loading and applying using groundboom equipment is not considered to be acceptable considering PPE as specified on certain end use product labels. For consistency and to improve clarity, updates to the PPE requirements are proposed, and the potential risk to workers mixing, loading, and applying bromoxynil using ground equipment is considered to be acceptable with the updated PPEs (Appendix V);

- Potential risks to workers mixing/loading for aerial applications and to workers applying using aerial application equipment are considered to be acceptable under current conditions of use. No additional risk mitigation measures are required; and

- Potential risks to postapplication workers are considered to be acceptable for all sites/activities at the REI (24 hours) specified on current labels, with the exception of workers involved in handset irrigation (sweet corn and garlic) and hand harvesting (sweet corn). To mitigate potential risks for workers using handset irrigation (sweet corn and garlic) and hand harvesting (sweet corn), additional mitigation measures (REIs) are proposed (Appendix V).

In addition, in order to improve clarity of the end-use product labels, specific use directions (two applications at a minimum re-treatment interval of 21 days) are proposed to be included for established alfalfa and corn. The proposed label amendments are summarized in Appendix V.

4.5 Characterization of Potential Risk to the Aquatic Environment

As part of this special review, potential risk to non-target aquatic organisms resulting from applications of bromoxynil was assessed using available information (Canada, 2008a; Canada, 2008b; United States, 2013a; United States 2013b). When used as directed, bromoxynil can enter the environment following application to agricultural fields and grasslands. Non-target aquatic habitats may be exposed to residues of bromoxynil as a result of spray drift and/or runoff.

Bromoxynil octanoate is not expected to persist in the environment: the esters dissipate rapidly in the aerobic environment (aerobic soil biotransformation half-life = 2 days; aerobic aquatic half-life = 0.6 days) to the phenol form which further degrades to CO_2. Bromoxynil octanoate is expected to be slightly mobile in soil based on its soil adsorption characteristics. If bromoxynil enters water through spray drift or runoff, it is not expected to remain as it is regarded as non-persistent in aquatic systems.

Toxicity studies indicate that bromoxynil is very highly acutely toxic to freshwater fish (bluegill sunfish LC_{50} = 29 µg/L), and the chronic no observed effect concentration (NOEC) in fathead minnows is 9 µg/L. With respect to freshwater aquatic invertebrates, studies suggest that bromoxynil is also very highly acutely toxic to aquatic invertebrates (*Daphnia pulex* EC_{50} = 11µg/L), and the chronic aquatic invertebrate NOEC is 2.5 µg/L (*Daphnia magna*). Acute studies show that bromoxynil was found to be highly toxic to estuarine/marine fish (sheepshead minnow, LC_{50} = 170 µg/L) and very highly toxic to estuarine/marine invertebrates (Mysid shrimp, LC_{50} = 65 µg/L). For aquatic algae and diatoms, the most sensitive EC_{50} was 51µg/L (*Navicula pelliculosa*), and for vascular aquatic plants (*Lemma gibba),* the EC_{50} was 219 µg/L.

Potential risk of bromoxynil to aquatic organisms: An environmental risk assessment integrates environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of a pesticide in various environmental media, such as water. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties, and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information used to establish reference endpoints includes acute and chronic toxicity data for various organisms or groups of organisms from aquatic habitats including invertebrates, vertebrates, and plants.

Initially, a conservative screening-level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, application at a maximum cumulative application rate), and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the EEC with an appropriate toxicity value (RQ = exposure/toxicity). The RQ is then compared to the PMRA's level of concern for aquatic organisms (LOC = 1).

Screening level RQs (direct overspray to the aquatic environment) were exceeded for the aquatic risk assessment: risk quotients based on the most sensitive aquatic endpoints ranged from 1 to 25. Therefore, risk to aquatic habitats via both runoff and spray drift were characterised separately.

The EECs in water from runoff (EEC for acute risk is 10 µg a.i./L; EEC for chronic risk is 1.0 µg a.i./L) was modeled using the Generic Estimated Environmental Concentration Program (GENEEC) (Canada, 2008a) based on conservative fate parameters and application rates. In addition, the PMRA considered the available surface water monitoring information, and, the maximum concentration of bromoxynil measured in Canadian waters (18 µg a.i./L) was compared to aquatic toxicity values. All RQs based on the concentration of bromoxynil from runoff (modelled and monitoring information) were <10. Based on the Canadian use pattern (ground and aerial application), risk to aquatic organisms from spray drift was also characterised. This assessment was based on the maximum cumulative application rate for bromoxynil on Canadian labels and deposition of pesticide residues at 1 m downwind from the site of application. For all crop/application scenarios, RQs (based on spray drift) were <2.

To minimize exposure of bromoxynil to the aquatic environment, current end-use product labels include information on best practices to minimize runoff following application as well as buffer zones (Appendix IV) to mitigate the potential risk from spray drift. As such and based on the available information, potential risk to non-target aquatic organisms from the use of bromoxynil is considered acceptable when current label directions are followed. No further risk mitigation measures are proposed.

To meet the current labelling standard and for consistency, updates to the aquatic toxicity statement, the runoff statements, and use directions are proposed. (Appendix V).

5.0 Incident Reports

The PMRA incident reporting database was searched for incident reports related to the identified aspects of concern for bromoxynil. As of 28 May 2018, the PMRA has received 12 human and one environmental incident report(s) involving bromoxynil which were related to the identified aspects of concern specific to occupational health risk (mixing, loading and/or applying) and the environment. No incident reports were related to carcinogenicity or developmental effects.

The 12 incidents were relevant to the occupational health risk occurred in Canada. They were classified as minor in severity, and all, except one, involved other active ingredients in addition to bromoxynil. The lone incident involving only bromoxynil reported an applicator being sprayed

in the face with the concentrated product. Ocular, oral, and dermal exposures were reported along with minor symptoms including pharyngolaryngeal pain, paresthesia, and nausea. All symptoms resolved within 24 hours. The other 11 occupational incidents included bromoxynil and other active ingredients with various exposure scenarios.

One environmental incident was relevant to the aquatic risk. The incident was of major severity and occurred in Canada: water used to douse a fire at a chemical distribution warehouse entered a stream and was followed by the mortality of a large number of fish. However, bromoxynil was considered unlikely to have contributed to the fish mortality as water samples contained the presence of several other pesticide ingredients, and the concentration of bromoxynil detected was not expected to have caused the fish mortality.

Overall, no human health or environmental concerns were identified in the incident reports when products are used according to current label directions. Therefore, no additional risk mitigation measures were proposed as a result of these incidents.

6.0 Proposed Special Review Decision for Bromoxynil

Evaluation of available scientific information related to the aspects of concern indicates that the potential dietary and non-occupational risks to human health and the potential risk to non-target aquatic organisms are considered acceptable under the current conditions of use. No additional risk mitigation measures are proposed. However, to meet the current labelling standard and for consistency, updates to the aquatic toxicity statement, the runoff statements, and use directions are proposed.

The assessments indicate that the potential occupational risk to workers mixing and loading for aerial application and to workers applying bromoxynil using aerial equipment are considered to be acceptable with the current label directions. No additional risk reduction measures are proposed.

The potential occupational risk to workers mixing, loading, and applying bromoxynil using groundboom equipment is not considered to be acceptable with PPE as specified on certain end use product labels. For consistency and to improve clarity, updates to the PPE requirements are proposed. Potential risk to workers mixing, loading, and applying bromoxynil using ground equipment is considered acceptable with the updated PPE.

The potential risks to postapplication workers are considered to be acceptable for all sites/activities under the current conditions of use, with the exception of workers involved in certain activities (handset irrigation in sweet corn and garlic and hand harvesting in sweet corn). Therefore, additional risk reduction measures are proposed to mitigate potential risks for workers performing handset irrigation (sweet corn and garlic) and hand harvesting (sweet corn). With the proposed additional risk reduction measures (REIs), potential risk to post application workers performing handset irrigation in sweet corn and garlic, as well as hand harvesting in sweet corn, is considered acceptable.

On this basis, Health Canada's Pest Management Regulatory Agency, pursuant to subsection 21(1) of *the Pest Control Product Act*, is proposing continued registration of bromoxynil products for sale and use in Canada with additional mitigation measures. The proposed label amendments are summarized in Appendix V.

This proposed special review decision is a consultation document.[1] The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. All comments are to be directed to Publications (contact information on the cover page of this document).

7.0 Next Steps

Before making a final decision on the special review of bromoxynil, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on bromoxynil. The PMRA will then publish a special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed decision, and the PMRA's response to these comments.

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

List of Abbreviations

ADI	Acceptable Daily Intake
AHETF	Agricultural Handlers Exposure Task Force
ARfD	Acute Reference Dose
ARTF	Agricultural Re-Entry Rask Force
ATPD	Area Treated per Day
CAF	Composite Assessment Factor
CAR	Constitutive Androstane Receptor
CDC	Centers for Disease Control and Prevention
CO_2	Carbon Dioxide
DBHA	3,5-dibromo-4-hydroxybenzoic acid
DEEM-FCID™	Dietary Exposure Evaluation Model - Food Commodity Intake Database™
DFR	Dislodgeable Foliar Residues
EC_{50}	Effect Concentration, 50%
EEC	Estimated Environmental Concentration
GENEEC	Generic Estimated Environmental Concentration Program
LC_{50}	Lethal Concentration, 50%
LOC	Level of Concern
M/L/A	Mixer/Loader/Applicator
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
NCHS	National Center for Health Statistics
NHANES/ WWEIA	National Health and Nutritional Examination Survey, What We Eat in America
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPARα	Peroxisome Proliferator-Activated Receptor Alpha
PPE	Personal protective Equipment
PRZM GW	Pesticide Root Zone Model Groundwater
REI	Restricted Entry Interval
RQ	Risk Quotient
SWCC	Surface Water Concentration Calculator
TC	Transfer Coefficient
USEPA	United States Environmental Protection Agency

Appendix I Registered products containing Bromoxynil as of 26 October 2018

Pest Control Product No.	Class	Registrant	Product Name	Formulation	Guarantee
16164	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BADGE EMULSIFIABLE SELECTIVE WEEDKILLER	EMULSIFIABLE CONCENTRATE	MCPA, 225 g/L BROMOXYNIL, 225 g/L
18001	Commercial	BAYER CROPSCIENCE INC	PARDNER HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-280 g/L
18022	Commercial	BAYER CROPSCIENCE INC	BUCTRIL M	EMULSIFIABLE CONCENTRATE	MCPA-280 g/L BROMOXYNIL-280 g/L
22659	Commercial	BAYER CROPSCIENCE INC	THUMPER EMULSIFIABLE SELECTIVE WEEDKILLER	EMULSIFIABLE CONCENTRATE	2,4-D-280 g/L BROMOXYNIL-280 g/L
25341	Commercial	NUFARM AGRICULTURE INC.	NUFARM KORIL 235 LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-235 g/L
25791	Commercial	BAYER CROPSCIENCE INC	COMPAS 480 EC HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-480 g/L
26999	Commercial	NUFARM AGRICULTURE INC.	MEXTROL 450 LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
28109	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	IPCO LOGIC M LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
28123	Commercial	NUFARM AGRICULTURE INC.	APPROVE HERBICIDE	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
28276	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BROMOTRIL 240 EC	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
28519	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	IPCO BROTEX 240 LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
28738	Commercial	BAYER CROPSCIENCE INC	INFINITY HERBICIDE	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE-37.5 g/L BROMOXYNIL-210 g/L
28779	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	THRASHER	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
28853	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	IPCO LEADER LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
28876	Commercial	NUFARM AGRICULTURE INC.	BENCHMARK B HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-235 g/L
28947	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	IPCO LEADER 450 LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
29051	Commercial	BAYER CROPSCIENCE INC	VELOCITY 2 HERBICIDE	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE-37.5 g/L BROMOXYNIL-210 g/L
29214	Commercial	BAYER CROPSCIENCE INC	VELOCITY B HERBICIDE	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE-37.5 g/L BROMOXYNIL-210 g/L
29367	Commercial	BAYER	TUNDRA HERBICIDE	EMULSIFIABLE	PYRASULFOTOLE-15.5 g/L

		CROPSCIENCE INC		CONCENTRATE	FENOXAPROP-P-ETHYL-46 g/L BROMOXYNIL-87.5 g/L
29510	Commercial	BAYER CROPSCIENCE INC	BRY-MAE 2 HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA-280 g/L BROMOXYNIL-280 g/L
29513	Commercial	BAYER CROPSCIENCE INC	THUMPER TOTAL 2 HERBICIDE	EMULSIFIABLE CONCENTRATE	2,4-D-280 g/L BROMOXYNIL-280 g/L
29584	Commercial	BAYER CROPSCIENCE INC	VELOCITY M3 ALL-IN-ONE HERBICIDE	SUSPENSION	THIENCARBAZONE-METHYL-5 g/L PYRASULFOTOLE-31.3 g/L BROMOXYNIL-175 g/L
30005	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	WEEDAWAY LEADER HERBICIDE	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
30007	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	INT-110 HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA- g/L BROMOXYNIL-225 g/L
30008	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	WEEDAWAY LOGIC M HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
30009	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	INT-111 HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
30010	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	WEEDAWAY BROTEX 240 HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
30370	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BADGE II	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
30371	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BROMOTRIL 11 240 EC	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-235 g/L
30372	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	THRASHER II	EMULSIFIABLE CONCENTRATE	2,4-D-225 g/L BROMOXYNIL-225 g/L
30690	Commercial	NUFARM AGRICULTURE INC.	ENFORCER D HERBICIDE	EMULSIFIABLE CONCENTRATE	FLUROXYPYR-80 g a.e./L 2,4-D-240 g/L BROMOXYNIL-190 g/L
30691	Commercial	NUFARM AGRICULTURE INC.	ENFORCER M HERBICIDE	EMULSIFIABLE CONCENTRATE	MCPA-200 g/L FLUROXYPYR-80 g a.e./L BROMOXYNIL-200 g/L
31348	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	IPCO BROTEX 480 LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-480 g/L
31429	Commercial	INTERPROVINCIAL COOPERATIVE LIMITED	WEEDAWAY BROTEX 480	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-480 g/L
31431	Commercial	LOVELAND PRODUCTS CANADA INC.	BROMAX TM LIQUID HERBICIDE	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-480 g/L
31992	Commercial	BAYER CROPSCIENCE INC	RRRPSABRY HERBICIDE	SUSPENSION	THIENCARBAZONE-METHYL-5 g/L PYRASULFOTOLE-31.3 g/L BROMOXYNIL-175.0 g/L
32260	Commercial	BAYER CROPSCIENCE INC	PSABRY HERBICIDE	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE-37.5 g/L BROMOXYNIL-210 g/L
32472	Commercial	ALBAUGH LLC	BROMOXYNIL-MCPA 225-225	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L

32528	Commercial	NUFARM AGRICULTURE INC.	CONQUER HERBICIDE	EMULSIFIABLE CONCENTRATE	PYRAFLUFEN-ETHYL-15 g/L BROMOXYNIL-467 g/L
32607	Commercial	BAYER CROPSCIENCE INC	RRRPSABRY-SP HERBICIDE	SUSPENSION	THIENCARBAZONE-METHYL-5 g/L PYRASULFOTOLE-31.3 g/L BROMOXYNIL-175 g/L
32622	Commercial	ALBAUGH LLC	BROMOXYNIL 240 EC	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
32681	Commercial	SYNGENTA CANADA INC.	A19278	EMULSIFIABLE CONCENTRATE	BICYCLOPYRONE-37.5 g/L BROMOXYNIL-175 g/L
32685	Commercial	NEWAGCO INC	MPOWER BUCK M	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
32911	Commercial	NEWAGCO INC	MPOWER BROMOXYNIL	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
24403	Manufacture	BAYER CROPSCIENCE INC	BROMOXYNIL MIXED ESTER SOLUTION 50%	SOLUTION	BROMOXYNIL-50 g/L
24404	Manufacture	BAYER CROPSCIENCE INC	BROMOXYNIL MIXED ESTER SOLUTION 60%	SOLUTION	BROMOXYNIL-60 g/L
24471	Manufacture	BAYER CROPSCIENCE INC	BROMOXYNIL MIXED ESTER SOLID	SOLID	BROMOXYNIL-66.3%
28696	Manufacture	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BROMOTRIL 240 MANUFACTURING USE PRODUCT	EMULSIFIABLE CONCENTRATE	BROMOXYNIL-240 g/L
28699	Manufacture	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BADGE MANUFACTURING USE PRODUCT	EMULSIFIABLE CONCENTRATE	MCPA-225 g/L BROMOXYNIL-225 g/L
28864	Manufacture	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BROMOTRIL MANUFACTURING CONCENTRATE	SOLUTION	BROMOXYNIL-56.2 g/L
29413	Manufacture	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL ME 50	SOLUTION	BROMOXYNIL-50 g/L
29414	Manufacture	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL ME 60	SOLUTION	BROMOXYNIL-60 g/L
29415	Manufacture	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL ME SOLID	SOLID	BROMOXYNIL-66.8%
33190	Manufacture	BAYER CROPSCIENCE INC	INFINITY MANUFACTURING	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE-37.5 g/L BROMOXYNIL-210 g/L
33229	Manufacture	BAYER CROPSCIENCE INC	PSABRYFPF MANUFACTURING	EMULSIFIABLE CONCENTRATE	PYRASULFOTOLE -15.5 g/L FENOXAPROP-P-ETHYL -46 g/L BROMOXYNIL-87.5 g/L
19693	Technical	BAYER CROPSCIENCE INC	BROMOXYNIL TECHNICAL	SOLID	BROMOXYNIL-92.5% (CAS# 1689-99-2)
19700	Technical	BAYER CROPSCIENCE INC	BROMOXYNIL HEPTANOATE TECHNICAL	SOLID	BROMOXYNIL-68.2% (CAS# 56634-95-8)
19705	Technical	BAYER CROPSCIENCE INC	BROMOXYNIL OCTANOATE TECHNICAL	SOLID	BROMOXYNIL-65.9% (CAS# 1689-99-2)
21926	Technical	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL PHENOL	SOLID	BROMOXYNIL-92.5% (CAS# 1699-84-5)
21927	Technical	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL OCTANOATE TECHNICAL	SOLID	BROMOXYNIL-65.5% (CAS# 1689-99-2)

27675	Technical	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	BROMOTRIL TECHNICAL	SOLID	BROMOXYNIL-66.1% (CAS# 1689-99-2)
29412	Technical	NUFARM AGRICULTURE INC.	NUFARM BROMOXYNIL HEPTANOATE TECHNICAL	SOLID	BROMOXYNIL-68.2% (CAS# 56634-95-8)
31987	Technical	NEWAGCO INC	BROMOXYNIL HEP TECHNICAL HERBICIDE	SOLID	BROMOXYNIL-70.85% (CAS# 56634-95-8)
31988	Technical	NEWAGCO INC	BROMOXYNIL OCT TECHNICAL HERBICIDE	SOLID	BROMOXYNIL-68.5% (CAS# 1689-99-2)
32470	Technical	ALBAUGH LLC	ALBAUGH BROMOXYNIL OCTANOATE TECHNICAL	SOLID	BROMOXYNIL-67.2% (CAS# 1689-99-2)
32592	Technical	BAYER CROPSCIENCE INC	BROMOXYNIL MIXED ESTER TECHNICAL	SOLID	BROMOXYNIL-66.5% (CAS# 1689-99-2)

Appendix II Toxicological Reference Values for Use in the Human Health Risk Assessment

Following the initiation of the special review, the PMRA conducted a review of the available toxicology data and established and /or confirmed toxicological reference values (Table 1). As bromoxynil phenol and bromoxynil octanoate have been determined to be toxicologically equivalent, studies on both forms were considered in the assessment. The hazard database for bromoxynil is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes.

Acute Reference Dose (ARfD) for Females 13-49 Years of Age

To estimate acute dietary risk, the NOAEL of 5 mg/kg bw/day based on the collective evidence from oral developmental toxicity studies in rats was selected for the point of departure. An increase in the incidence of supernumerary ribs was the most sensitive endpoint in these studies occurring at 12 mg/kg bw/day and above. The frequency of supernumerary ribs can be affected by a narrow window of exposure during development. For this reason, this variation was considered relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied. The PCPA factor was reduced to onefold based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section (Section 4.2). Thus, the composite assessment factor (CAF) is 100. The ARfD for females 13-49 years of age is 0.05 mg/kg bw. This point of departure provides a margin of 600 to the NOAEL of 30 mg/kg bw/day for malformations in the rabbit developmental toxicity study, and a margin of 900 to the effect level.

ARfD for the General Population (excluding females 13-49 years of age)

To estimate acute dietary risk, an endpoint from the 90-day oral toxicity study in the dog was selected for the point of departure. A NOAEL of 8 mg/kg bw was established in the study for clinical signs seen after administration of the first dose at 12 mg/kg bw and above. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied. The PCPA factor was reduced to onefold based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section (Section 4.2). Thus, the CAF is 100. The ARfD for the general population (excluding females 13-49 years of age) is 0.08 mg/kg bw.

Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the NOAEL of 0.3 mg/kg bw/day from a 1-year oral toxicity study in the dog was selected. An increase in clinical signs and liver weight and decreases in body weight and body weight gain were observed at 1.5 mg/kg bw/day and above. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied. The PCPA factor was reduced to onefold based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section (Section 4.2).

Thus, the CAF is 100. The ADI is 0.003 mg/kg bw/day. The endpoint selected for non-cancer risk assessment is protective of any residual concerns regarding the oncogenic potential of bromoxynil.

Short-/Intermediate-term Dermal

For short- and intermediate-term exposure via the dermal route, the NOAEL of 10 mg/kg bw/day from the dermal developmental toxicity study in the rat was selected as the point of departure. An increase in supernumerary ribs was observed at 50 mg/kg bw/day and above. The selection of this endpoint was supported by a dermal developmental toxicity study in the rat conducted with a formulation of bromoxynil octanoate that also had a NOAEL of 10 mg/kg bw/day based on an increased incidence of supernumerary ribs at 15 mg/kg bw/day. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied resulting in a target MOE of 100. For residential exposure, the PCPA factor was reduced to onefold based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section (Section 4.2). The endpoint selected for non-cancer risk assessment is protective of any residual concerns regarding the oncogenic potential of bromoxynil.

Short-/Intermediate-term Inhalation

For short- and intermediate-term exposure via the inhalation route, no route-specific studies were available. The NOAEL of 5 mg/kg bw/day was selected for the point of departure, based on an increased incidence of supernumerary ribs in the collective evidence from oral developmental toxicity studies in rats. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied resulting in a target MOE of 100. For residential exposure, the PCPA factor was reduced to onefold based on the rationale provided in the *Pest Control Products Act* Hazard Characterization section (Section 4.2). The endpoint selected for non-cancer risk assessment is protective of any residual concerns regarding the oncogenic potential of bromoxynil.

Table 1 Toxicological Reference Values for Use in Health Risk Assessment for Bromoxynil

Exposure Scenario	Endpoint	Study/Point of departure	MOE/CAF [a]
Acute dietary - females 13 -49 years of age	↑ incidence of supernumerary ribs	Collection of oral developmental toxicity studies in rats NOAEL 5 mg/kg bw/day	100
Acute dietary - general population (excluding females 13-49 years of age)	Clinical signs	Oral toxicity 90-day study in dogs Single dose NOAEL 8 mg/kg bw/day	100
ARfD = 0.05 mg/kg bw (females 13-49 years of age) 0.08 mg/kg bw (general population, excluding females 13-49 years of age)			
Repeated dietary - general population	Clinical signs, ↓ bw and bwg, ↑ liver wt.	1-year oral toxicity study in dogs NOAEL 0.3 mg/kg bw/day	100
ADI = 0.003 mg/kg bw/day			

Short/Intermediate-term dermal	↑ incidence of supernumerary ribs	Dermal developmental toxicity study in rats NOAEL 10 mg/kg bw/day	100
Short/Intermediate-term inhalation[1]	↑ incidence of supernumerary ribs	Collection of oral developmental toxicity studies in rats NOAEL 5 mg/kg bw/day	100
Cancer Endpoint	Evidence of liver tumours in mice. The endpoint selected for non-cancer risk assessment is protective of any residual concerns regarding the oncogenic potential of bromoxynil.		

[a] CAF (composite assessment factor) refers to total of uncertainty and PCPA factors for dietary assessments; MOE (margin of exposure) refers to a target margin of exposure for occupational and residential assessments

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

Appendix III Occupational Risk Assessment for Bromoxynil

Table 1 Mixer, Loader, and Applicator Exposure and Risk Assessment for Bromoxynil

Scenario	Unit Exposure (mg/kg a.e.)		Area Treated Per Day (ha/day)	Application Rate (kg a.e./ha)	Active Handled Per Day (kg a.e./ day)	Daily Exposure Dose[a] (mg/kg bw/day)		Dermal MOE[b]	Inhalation MOE[c]	Combined MOE[d]
	Dermal	Inhalation				Dermal	Inhalation			
LIQUID, Open Mixing/Loading + groundboom application, OPEN CAB										
MLA: Single layer plus chemical-resistant gloves	0.084	0.002	360	0.3525	126.90	0.1331	0.00366	75	1365	71
M/L: Cotton coveralls over single layer plus chemical-resistant gloves A: Single layer plus chemical-resistant gloves	0.057	0.002	360	0.3525	126.9	0.0900	0.0037	111	1365	103
LIQUID, Open Mixing/Loading + groundboom application, CLOSED CAB										
MLA: Single layer plus chemical-resistant gloves	0.070	0.001	360	0.3525	126.90	0.1103	0.00109	91	4568	89
M/L: Cotton coveralls over single layer plus chemical-resistant gloves A: Single layer	0.042	0.001	360	0.3525	126.9	0.0672	0.0011	149	4568	144
LIQUID, Open Mixing/Loading for aerial application										
Cotton coveralls over single layer plus chemical-resistant gloves	0.031	0.001	400	0.336	134.4	0.0526	0.0011	190	4724	183
Aerial Application										
Single layer	0.003	0.00001	400	0.336	134.4	0.0045	0.0000	2229	307140	2213

[a] Daily Exposure Dose (mg/kg bw/day) = Unit Exposure (mg/kg a.i.) × ATPD (ha) × Application rate (kg a.i./ha) × / Average worker Body weight (80kg)

[b] Dermal MOE - Based on a NOAEL of 10 mg/kg bw/day, target MOE = 100

[c] Inhalation MOE - Based on a NOAEL of 5 mg/kg bw/day, target MOE = 100

[d] Combined MOE = $1/((1/MOE_{dermal}) + (1/MOE_{inhalation}))$, target MOE 100

Table 2 Postapplication Occupational Exposure and Risk Assessment for Bromoxynil

Crop[a]	Application Rate (kg a.e./ha)	No. of Applications	Application Interval (days)	Activity[b]	Transfer coefficient[c] (cm^2/hr)	DFR[d] (ug a.e./cm^2)	Daily Dermal Exposure[e] (mg/kg bw/day)	MOE[f]	REI (days)
GRASSES AND FIELD CROPS (Alfalfa, Corn (field), Seedling Grasses, Canary Seed)	0.336	2	21	Scouting	1100	0.94	0.1034	97	-
FIELD CROPS (Barley, Rye, Oats, Wheat, Flax)	0.336	1	-	Scouting	1100	0.85	0.0935	107	-
CORN (sweet)	0.336	2	21	Harvest (hand)	8800	0.94	0.8272	12	20
				Irrigation (hand)	1750		0.1645	61	5
				Scouting	1100		0.1034	97	-

ONION (dry bulb only)	0.144	2	10	Irrigation (hand)	1750	0.49	0.0858	117	-
				Scouting & Thinning	1300		0.0637	157	-
GARLIC	0.288	1	-	Irrigation (hand)	1750	0.725	0.1269	79	2
				Scouting & Thinning	1300		0.0943	106	-

[a] Use on canola and carrots was not considered in the postapplication assessment as label-specified use is restricted to pre-seed/ pre-plant / pre-emergence

[b] Activities such as weeding were not considered as it is not an expected postapplication activity following use of an herbicide. Hand harvesting of both garlic and onions was also not considered because current label indicates a pre-harvest interval of 58 and 75 days, respective

[c] Transfer coefficients (TC) from Agricultural Re-entry Task Force (ARTF)

[d] Dislodgeable Foliar Residue (DFR) = 25% residue deposition with a 10% residue dissipation/day

[e] Daily Dermal Exposure (mg/kg bw/day) = TC (cm^2/hr) × DFR (mg a.e./cm^2) × 8 hours/day / average worker body weight (80kg)

[f] MOE - Based on a NOAEL of 10 mg/kg bw/day, target MOE = 100

Appendix IV Buffer Zone Label Requirements

Method of Application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1m	Greater than 1m	Less than 1m	Greater than 1m
Field sprayer*	All crops		1	1	1	1
Aerial	Oats	Fixed wing	15	2	1	1
		Rotary wing	15	1	1	1
	Barley and wheat	Fixed wing	20	5	1	1
		Rotary wing	20	3	1	1

* For field sprayer application, buffer zones can be reduced with the use of drift-reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

Appendix V Proposed End-Use Product Label Amendments

The label amendments presented below represent label recommendations for bromoxynil only. Co-formulants are not addressed in this special review, and it does not include all label requirements for individual end-use products (for example, supplementary protective equipment, first aid statements, disposal statements, and precautionary statements). Information on labels of currently registered products should not be removed unless it contradicts the below label statements. Please read each section carefully and make appropriate changes to your product labels.

I) For consistency and to meet the current labelling standard, the following are proposed to be included a section entitled **PRECAUTIONS**:

"Do not use in residential areas, which are defined as sites where bystanders may be present during or after spraying, including homes, schools, parks, playgrounds, playing fields, and public buildings."

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."

II) The existing information on personal protective equipment are proposed to be revised as below in a section entitled **PRECAUTIONS**:

***"Ground applications:** Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, clean-up and repair. Wear a long-sleeved shirt and long pants, chemical resistant gloves, and socks plus shoes during applications. Gloves are not required during application within a closed cab."*

***"Aerial applications: the field crew and the mixer/loaders:** Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."*

*"**Aerial applicators**: Wear a long-sleeved shirt, long pants, socks and shoes during application. Gloves are not required during application within a closed cockpit. Do not allow the pilot to mix chemicals to be loaded onto the aircraft."*

III) The existing information on restricted entry intervals are proposed to be revised as below in a section entitled **PRECAUTIONS**:

***"DO NOT** enter or allow worker entry into treated areas during the restricted entry intervals (REIs) specified in the following table:*

CROP	*ACTIVITY*	*REI (days)*

Garlic	*Irrigation, handset*	*2*
Sweet Corn	*Irrigation, handset*	*5*
	Harvest, hand	*20*

*For all other postapplication activities, **DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 24 hours."*

IV) For clarity for labels with approved use for two applications at 336 g a.e./ha on CORN (Field & Sweet), the following are proposed to be included in a section entitled **DIRECTIONS FOR USE**:

"Corn may be treated with a broadcast post-emergence application at the recommended rate from the 4-leaf stage onward. To ensure adequate coverage of weeds, drop pipes should be used when corn is beyond the 8-leaf stage or for a second application for later germinating weeds such as cocklebur and velvetleaf. Minimum re-treatment interval for the second application is 21 days. For hand harvesting, re-entry is not permitted until 20 days after application. As such, a pre-harvest interval (PHI) of 20 days after application is required. For handheld irrigation, re-entry is not permitted until 5 days after application."

V) For clarity for labels with approved use for two applications at 336 g a.e./ha on ESTABLISHED ALFALFA (for seed production only, Provinces of Alberta, Saskatchewan, Manitoba only), the following are proposed to be included in a section entitled **DIRECTIONS FOR USE**:

"Established alfalfa may be treated until alfalfa is 25 cm tall. Maximum of 2 applications per year. Minimum re-treatment interval for the second application is 21 days."

VI) For consistency and to meet the current labelling standard, the following statements are proposed to be included in a section entitled **DIRECTIONS FOR USE:**

"As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

VII) For consistency and to meet the current labelling standard, the following statements are proposed to be included in a section entitled **ENVIRONMENTAL PRECAUTIONS:**

"Toxic to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE."

"To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay."

"Avoid application when heavy rain is forecast."

"Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body."

References

I) Information Considered in the Special Review not Supplied by Registrant

Published

PMRA Document Number	Reference
1545421	Canada 2008a. Proposed Re-evaluation Decision: Bromoxynil. PRVD2008-07
1605164	Canada, 2008b. Re-evaluation Decision: Bromoxynil. RVD2008-21
2405939	Canada, 2013. Pest Management Regulatory Agency Regulatory Note: Special Review Initiation of 23 Active Ingredients. REV2013-06
2930001	United States, 2013a. EFED Registration Review Problem Formulation for Bromoxynil and Bromoxynil Esters. January 22nd, 2013.
2930004	United States, 2013b. Bromoxynil Final Work Plan. September 2013
2930002	Rotterdam Convention, December 2001. Prior Informed Consent Circular XIV.
1307568	I. Giroux, 1999, Contamination de l'eau par les pesticides dans les régions de culture de maïs et de soya au Québec, Campagnes d'échantillonnage de 1996, 1997 et 1998, ministère de l'Environnement, Direction des écosystèmes aquatiques, QuaIité de l'eau, DACO: 8.6
1307571	I. Giroux, 2002, Contamination de l'eau par les pesticides dans les régions de culture de maïs et de soya au Québec, Campagnes d'échantillonnage de 1999, 2000 et 2001 et évolution temporelle de 1992 à 2001, ministère de l'Environnement, Direction du suivi de l'état de l'environnement, Envirodoq ENV/2002/0365, QE/137, DACO: 8.6
1307572	A.-M. Anderson, K.A. Saffran, G. Byrtus, D.O. Trew, R.D. Neilson, N.D. MacAlpine and R. Borg, 1998, Impacts of agriculture on surface water quality in Alberta, Part III: Pesticides in small streams and lakes, Prepared for CAESA Water Quality Committee, Published by Alberta Agriculture, Food and Rural Development, Edmonton, Canada - Alberta Environmentally Sustainable Agriculture Agreement, DACO: 8.6
1307573	R.S. Currie and D.A. Williamson, 1995, An assessment of pesticide residues in surface waters of Manitoba, Canada. Water Quality Management Section, Manitoba Environment, Canada - Manitoba Agreement on Agricultural Sustainability, DACO: 8.6
1307581	I. Giroux, 1998, Impact de l'utilisation des pesticides sur la qualité de l'eau des bassins versants des rivières Yamaska, L'Assomption, Chaudière et Boyer, ministère de l'Environnement et de la Faune, Direction des écosystèmes aquatiques, dans le contexte de Saint-Laurent Vision 2000, Saint-Laurent - Vision 2000, 48 p., DACO: 8.6

1307590 Anderson, A_M., 1995, CAESA, Overview of Pesticide Data for Alberta Surface Waters. Appendix A4. Phase 2 Selection of Soil Landscape Units and Study Design Considerations for the Surface Water Quality Monitoring, CAESA, DACO: 8.6

1307591 STRUGER, J., S. LITALIEN AND E. SVERKO, 2003, ENVIRONMENT CANADA, ECOSYSTEM HEALTH DIVISION, ENVIRONMENTAL CONSERVATION BRANCH, ONTARIO REGION., IN-USE PESTICIDE CONCENTRATIONS IN SURFACE WATERS OF THE LAURENTIAN GREAT LAKES, 1994 - 2000., DACO: 8.6

1345581 Rawn, D.F.K. et al, Pesticides in the Red River and its Tributaries in Southern Manitoba:1993-95. IN: Water Qual. Res. J. Canada. 1999. Vol. 34, No. 2. 183-219., DACO: 8.6

1398451 I. Giroux, C. Robert and N. Dassylva, 2006, Part 1: La présence de pesticides dans l'eau au Québec, Bilan dans les cours d'eau de zones en culture de maïs et de soya en 2002, 2003 et 2004 et dans les réseaux de distribution d'eau potable., Envirodoq No.ENV/2006/013, collection No. QE/00173, DACO: 8.6

1398452 I. Giroux, C. Robert and N. Dassylva, 2006, Part 2: La présence de pesticides dans l'eau au Québec, Bilan dans les cours d'eau de zones en culture de maïs et de soya en 2002, 2003 et 2004 et dans les réseaux de distribution d'eau potable. Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi de l'état de l'environnement, Direction des politiques de l'eau et Centre d'expertise en analyse environnementale du Québec., Envirodoq No.ENV/2006/013, collection No. QE/00173, DACO: 8.6

1398453 I. Giroux, C. Robert and N. Dassylva, 2006, Part 3: La présence de pesticides dans l'eau au Québec, Bilan dans les cours d'eau de zones en culture de maïs et de soya en 2002, 2003 et 2004 et dans les réseaux de distribution d'eau potable. Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi de l'état de l'environnement, Direction des politiques de l'eau et Centre d'expertise en analyse environnementale du Québec., Envirodoq No.ENV/2006/013, collection No. QE/00173, DACO: 8.6

1758182 Donald, D.B., Cessna, A.J., Sverko, E., Glozier, N.E., 2007, Pesticides in surface drinking-water supplies of the Northern Great Plains. Environmental Health Perspectives, VOLUME 115, NUMBER 8, August 2007, DACO: 8.6

2102602 I. Giroux, 2010, Présence de pesticides dans l'eau au Québec - Bilan dans quatre courd d'eau de zones en culture de maïs et de soya en 2005, 2006 et 2007 et dans des réseaux de distribution d'eau potable. Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi de l'état de l'environnement., Gouvernement du Québec, DACO: 8.6

2306368 I. Giroux and L. Pelletier, 2012, Présence de pesticides dans l'eau du Québec : bilan dans quatre cours d'eau de zones en culture de maïs et de soya en 2008, 2009 et 2010. Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi de l'état de l'environnement., Gouvernement du Québec, DACO: 8.6

2561884 I. Giroux. 2015. Présence de pesticides dans l'eau au Québec: Portrait et tendances dans les zones de maïs et de soya - 2011 à 2014, Québec, Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques, Direction du suivi de l'état de l'environnement, ISBN 978-2-550-73603-5, Available: http://www.mddelcc.gouv.qc.ca/eau/flrivlac/pesticides.htm, DACO: 8.6

2873192 Cohen et al. 2010, Evaluation of Possible Carcinogenic Risk to Humans Based on Liver Tumors in Rodent Assays: The Two-Year Bioassay Is No Longer Necessary - Toxicologic Pathway, Volume 38, Pages 487 to 501

2873193 Holsapple et al 2006, Mode of Action in Relevance of Rodent Liver Tumors to Human Cancer Risk - Toxicological Sciences, Volume 89, Number 1, Pages 51 to 56

2873194 Beam 2011, A Bayesian Framework for the Analysis of the Peroxisome Proliferator-Activated Receptor Signaling Pathway.

2877522 Kavlock et al 1995, The effect of Acute Maternal Toxicity on Fetal Development in the Mouse. Teratogenesis, carcinogenesis and Mutagenesis 5:3-13

2880383 European Commission, 2016. Draft Renewal Assessment Report prepared according to the Commission Regulation (EC) Number 1107/2009 - Bromoxynil, Volume 3 - B.6 (AS)

2880382 United States, 2012. Bromoxynil. Human Health Assessment Scoping Document in Support of Registration Review.

2930003 NTP 2015. Nonneoplastic Lesion Atlas. https://ntp.niehs.nih.gov/nnl/hepatobiliary/liver/index.htm

2149078 Elliott, J. et al., 2011, (2010). Groundwater vulnerability to pesticide contamination in the Assiniboine Delta Aquifer. Environment Canada Pesticide Science Fund, DACO: 8.6

2544468 I. Giroux. 2014. Présence de pesticides dans l'eau au Québec - Zones de vergers et de pommes de terre, 2010 à 2012. Québec, Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques. Direction du suivi de l'état de l'environnement, ISBN 978-2-550-71747-8 (PDF), DACO: 8.6

1311123 2005, DIRECTION DU SUIVI DE L'ETAT DE L'ENVIRONNEMENT; DEVELOPPEMENT DURABLE, ENVIRONNEMENT ET PARCS QUEBEC, LES PESTICIDES UTILISES DANS LES ESPACES VERTS URBAINS; PRESENCE DANS L'EAU DES REJETS URBAINS ET DANS L'AIR AMBIANT, Blibiotheque national du Québec, ISBN 2-550-44907-X, Envirodoq No ENV/2005/0165, DACO: 8.6

Unpublished

PMRA Document Number	Reference
1311107	2004, UNPUBLISHED WATER MONITORING DATA COLLECTED IN RESERVOIRS OF THE PRAIRIE REGION (2003 - 2004). PESTICIDE SCIENCE FUND., DACO: 8.6
1311112	2004, ENVIRONMENT CANADA, UNPUBLISHED NATIONAL WATER MONITORING DATA. PESTICIDE SCIENCE FUND (2004)., DACO: 8.6
1311116	2004, ENVIRONMENT CANADA, UNPBULISHED WATER MONITORING DATA COLLECTED IN WETLANDS OF THE PRAIRIE REGION (2004). PESTICIDE SCIENCE FUND., DACO: 8.6
1311128	2000, MANITOBA CONSERVATION, UNPUBLISHED DATA ON DETECTIONS OF PESTICIDES IN MUNICIPAL WATER SUPPLIES (1981 - 1999), DACO: 8.6
1311130	2002, MANITOBA CONSERVATION, Manitoba Conservation (2002) Unpublished Water Monitoring Data Collected in Manitoba (1990 - 2001), DACO: 8.6
1311143	2004, Raw data for Byrtus et al., 2004, A summary of pesticide residue data from the Alberta Treated Water Survey, 1995-2003, Alberta Environment, Environmental Assurance Service, Edmonton, DACO: 8.6
1345586	Jones, G. et al, 1998, Water Quality in Farm and Recreational Surface Water Supplies of Southwestern Manitoba. 1995 Sampling Results., Manitoba Environment. Winnipeg, Manitoba. Report No. 98-05. 86 pp., DACO: 8.6
1357369	2005, Unpublished Water Monitoring Data Collected From Lake Huron Tributaries (2002), DACO: 8.6
1726642	Pesticide Science Fund Annual Report 2007-2008, DACO 8.6, 9.9, DACO: 8.6,9.9
2525751	Environment Canada. 2011. Presence and levels of priority pesticides in selected Canadian aquatic ecosystems. Water Science and Technology Directorate, Environment Canada. ISBN 978-1-100-18386-2. 111 pages., DACO: 8.6
2572745	AHETF, 2009. Report # AHE1003-1: Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading of Liquid Formulations.
1913109	AHETF, 2009. Report # AHE1004: Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays.
2172938	AHETF, 2012. Report # AHE1007: Agricultural Handler Exposure Scenario Monograph: Closed Cockpit Aerial Application of Liquid Sprays.

2115788 Agricultural Re-entry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.

2780519 2017, Unpublished surface water and groundwater monitoring data for bromoxynil from 2000-2016 submitted by the Ministère du Développement durable, de l'Environnement et de la Lutte contre les Changements climatiques in response to the PMRA's June 6, 2017 monitoring data request for active ingredients undergoing re-evaluation or special review, DACO: 8.6

2893526 2017, Unpublished pesticide drinking water monitoring data for the province of Quebec (2010 - 2014), DACO: 8.6

2834286 2017, Unpublished water monitoring data for pesticides in Great Lakes Tributaries, from 2002 to 2007., DACO: 8.6

2171036 Ontario Ministry of the Environment. (2010). Unpublished groundwater monitoring data from Ontario's Provincial Groundwater Monitoring Network. Received September 2011., DACO: 8.6

2834287 2017, Unpublished water monitoring data for pesticides in Great Lakes Tributaries, from 2007 to 2016, DACO: 8.6

2893537 2017, Unpublished pesticide surface water monitoring data for the province of Ontario (2000 - 2016), DACO: 8.6

2893536 2017, Unpublished pesticide drinking water monitoring data for the province of Ontario (2000 - 2017), DACO: 8.6

2893539 2017, Unpublished pesticide monitoring data in surface water from the Prairie Region of Canada (1999-2016), DACO: 8.6

2893534 2017, Unpublished pesticide monitoring data from the Province of Manitoba (2001-2016), DACO: 8.6

2839820 2017, Unpublished water monitoring data for pesticides in Saskatchewan groundwater, from 2009 to 2015, DACO: 8.6

2839819 2017, Unpublished water monitoring data for pesticides in Saskatchewan surface water and groundwater, from 2006 to 2017, DACO: 8.6

2839822 2017, Unpublished water monitoring data for pesticides in Albert irrigation water, from 2006 to 2016, DACO: 8.6

2893273 Unpublished pesticide monitoring data for surface and groundwater 2006-2007 and 2011-2016, DACO: 12.5,8.6

2893272 Unpublished pesticide monitoring data in surface and groundwater from the Pacific Region of Canada 2003 - 2014, DACO: 12.5,8.6

Information Considered in the Special Review Supplied by Registrant

Unpublished

PMRA Document Number	Reference
2768319	Summary of U.S. Monitoring Data for Bromoxynil
2791552	Environmental Canada ambient water data - combined data set
2791553	Environmental Canada ambient water data – Summary
1182972	ANALYSIS OF THE ENVIRONMENTAL FATE OF BROMOXYNIL OCTANOATE APPLIED TO CORN IN A STANDARD FARM POND SETTING, PREPARED BY HYDROQUAL, FEBRUARY 1991 (ROPC0011) [BROMOXYNIL]
1204054	OCTANOL/WATER PARTITION COEFFICIENTS AND SOLUBILITIES FOR BROMOXYNIL AND AMBIEN PRODUCTS. UNION CARBIDE INTERNAL CORRESPONDENCE-TO: W.DAVIS. FROM: A.CAMPBELL. DATE: MARCH 7,1985
1204057	LEACHING STUDIES WITH BROMOXYNIL OCTANOATE. M.PARKINS. DATE: FEBRUARY 3,1982.(854C51;29827)
204058	LEACHING STUDIES WITH BROMOXYNIL OCTANOATE AND BROMOXYNIL BUTYRATE. M.PARKINS. DATE: DECEMBER 3,1981.(854C51;30646)
1204062	BROMINAL: CONFINED ACCUMULATION STUDY ON ROTATIONAL CROPS FOLLOWING 14C-BROMOXYNIL OCTANOATE TREATMENT OF SANDY LOAM SOIL. K.HUHTANEN. DATE: OCTOBER 18,1984.(854R10;33251;V5229)
1247585	HERBIDICES: BROMOXYNIL--AN ANALYTICAL METHOD FOR THE DETERMINATION OF BROMOXYNIL RESIDUES IN WATER
1247588	ENVIR CHEM: SUMMARIES
1247596	LEACHING STUDIES WITH BROMOXYNIL OCTANOATE. M.PARKINS. DATE: FEBRUARY 3,1982.(854C51;29827;RR0317;RR317;REFERENCE 63) + COVER LETTER RE: USE OF REGISTRATION INFORMATION. DATED: APRIL 11,1984.
1247682	UPTAKE, DEPURATION, AND BIOCONCENTRATION OF 14C-BROMOXYNIL OCTANOATE BY CHANNEL CATFISH. M.PARKINS ET.AL. DATE: AUGUST 31,1982. (854C51;30648;RR0319;RR319;REFERENCE 68) + COVER LETTER RE: USE OF REGISTRATION INFORMATION. DATED: APRIL 11,1984.
1247694	THE BEHAVIOUR OF ACTIVE PLANT PROTECTION CHEMICALS IN

SOIL. BROMINAL, K.P. POLZHOFER, JUNE 19, 1975

1247705 THE BEHAVIOUR OF PLANT PROTECTION CHEMICALS IN SOIL. BROMOXYNIL. (GER.). K.POLZHOFER. HAMBURG 19.6.75.(OR/GERMANY/563E;OR0563;REFERENCE 70)

1247717 14C BROMOXYNIL FIELD ROTATIONAL CROP STUDY: THE POTENTIAL UPTAKE OF 14C BROMOXYNIL AND/OR ITS METABOLITES IN VARIOUS CROPS FROM SOIL TREATED WITH 14C BROMOXYNIL OCTANOATE. A.GEMMA ET.AL. OCTOBER 8,1982.(82/602/BHL/AG;82/055;RR#45;ASD82055;RR0045;REFERENCE 71)

1247728 BROMOXYNIL RESIDUES IN CORN SOIL, SILAGE, FODDER AND GRAIN. SPRING/SUMMER FIELD PROGRAMS 1981 D-1 & D-4. W.CHOW ET.AL. MAY 1982.(82/311/BHL/AG;82/032;82/76/BHL/AG;82/142/BHL/AG;1074;RR46;RR 0046;ASD82032;REFERENCE 72)

2768317 Comparison of Regulatory Estimates of Drinking Water Concentrations with Monitoring Data

2768408 [14C]-Bromoxynil-phenol: Adsorption to and desorption from five soils

2768409 Summary of study M-568266-01-1 - [14C]-Bromoxynil-phenol: adsorption to and desorption from five soils

1204073 RADIOCARBON BALANCE ANALYSIS & EXCRETION PATTERN FOLLOWING A SINGLE ORAL DOSE OF BROMOXYNIL...IN MALE RATS

1204039 BROMOXYNIL PHENOL ACUTE TOXICITY AND IRRITANCY STUDIES

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1204049 BROMOXYNIL PHENOL DERMAL SENSITIZATION STUDY IN THE GUINEA PIG

1247513 HBN HERBICIDES: BROMOXYNIL HEPTANOATE AND BROMOXYNIL OCTANOATE: ACUTE ORAL AND PERCUTANEOUS TOXICITIES IN THE RAT

1247516 BROMOXYNIL OCTANOATE ACUTE TOXICITY & IRRITANCY STUDY

1204048 BROMOXYNIL OCTANOATE DERMAL SENSITIZATION STUDY IN THE GUINEA PIG

1204050 BROMOXYNIL OCTANOATE DERMAL SENSITIZATION STUDY IN THE GUINEA PIG

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1170761	EVALN OF THE ONCOGENIC POTENTL OF BROMOXYNIL ADMIN IN THE DIET TO MICE FOR 18 CONSECUTIVE MONTHS (SEE BTCH 23). R PARENT ET.AL. DATE: DECEMBER 31, 1980. (BRY-MKSS-I)
1170762	EVALN OF THE ONCOGENIC POTENTL OF BROMOXYNIL ADMIN IN THE DIET TO MICE FOR 18 CONSECUTIVE MONTHS - APPENDICES TO BTCH 22. DATE: JANUARY 8, 1981. (BRY-MKSS-I)
1160499	ONCOGENICITY STUDY WITH BROMOXYNIL PHENOL IN MICE FINAL REPORT.(HWI6224-174;BRO-T3-94-1506)
1160500	ONCOGENICITY STUDY WITH BROMOXYNIL PHENOL IN MICE FINAL REPORT.(HWI6224-174;BRO-T3-94-1506)
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1170770	EVALN OF THE ONCOGENIC POT'L & CHRONIC TOX EFFECTS OF TECH BROMOXYNIL IN RATS - SEE BTCH 30-37 & ROLL 17:BTCH 1. P BECOL ET.AL. DATE: JANUARY 8, 1982. (BRY-MKSS-I)
1170772	APPENDIX I TO BATCH 29 - PROTOCOL. STUDY DIRECTOR: T RE. DATE: FEBRUARY 21, 1978. (5815)
1170774	APPENDIX II TO BATCH 29 - CLINICAL LAB METHODOLOGY
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1170783	APPENDIX VII TO BATCH 29 - FDRL PERSONNEL RESPONSIBILITIES. J BECCI ET.AL. DATE: 1982. (5815
1170786	APPENDIX VIII TO BATCH 29 - QUALITY ASSURANCE. STUDY DIRECTOR: T RE. DATE: APRIL 4, 1980. (5815/1201)

1175239	APPENDIX IX TO BATCH 29, ROLL 17 - PATHOLOGY (NOTE: INCORRECT BAMF ON FILM). DATE: 1982. (BRY-MBY-SI)
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2775778	Bayer CropScience LP - Mouse PPARalpha Assays