Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2000-05

Cymoxanil Technical Curzate® 60 DF

The active ingredient cymoxanil and the formulated product Curzate 60DF, containing cymoxanil for the control of late blight of potatoes in Canada, have been granted Section 17 temporary registrations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Curzate 60DF, a fungicide developed by DuPont Canada for use on potatoes, which contains the active ingredient cymoxanil effective against late blight. The product will be sold and used for the first time in Canada during the 2000 growing season.

DuPont Canada will be carrying out additional chemistry, toxicological, residue and efficacy studies as a condition of this temporary registration. Following the review of this new data, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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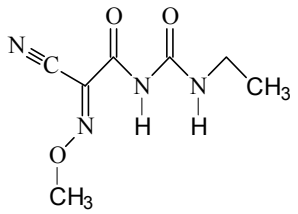
1.0 The active substance, its properties, uses, proposed classification and labelling

Cymoxanil is registered as a foliar-applied fungicide for potatoes and grapes in Europe. It is registered as a seed-piece treatment and as a foliar fungicide on potatoes in the United States (U.S.).

Curzate® 60 DF is a foliar fungicide for use on potatoes to control late blight. It may only be applied as a tankmix at 0.225 kg Curzate® 60 DF/ha (135 g active ingredient [a.i.]/ha) plus Manzate® 200 DF at 1.6 kg/ha (1.2 kg a.i./ha). Initial applications should start when local conditions indicate that late blight is imminent; make additional applications at five- to seven-day intervals. Apply no more than seven applications per crop. Do not apply within eight days of harvest.

1.1 Identity of the active substance and preparation containing it

Common name:	Cymoxanil
Function:	Fungicide
Chemical name:	
1. International Union of Pure and Applied Chemistry:	1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea
2. Chemical Abstracts Service (CAS):	(E)-2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide
CAS registry number:	57966-95-7
Molecular formula:	$C_7H_{10}N_4O_3$
Molecular weight:	198.2
Structural formula:	
Nominal purity of active:	96.8%
Identity of relevant impurities of toxicological, environmental and other significance:	The technical grade cymoxanil does not contain any impurities or microcontaminants known to be TSMP Track 1 substances

1.2 Physical and chemical properties of active substance

Technical product

Property	Result	Comment
Colour and physical state	Peach, solid	
Odour	Odourless	
Melting point or range	159–160EC	
Boiling point or range	Not applicable	
Density	1.32 g/mL	
Vapour pressure at 20EC	1.50×10^{-4} Pa (pure material)	Relatively nonvolatile
Henry's law constant at 20EC	1/H, 6.389×10^{7} K, 3.879×10^{-5} Pa•m^3/mole	Nonvolatile from moist soil and water surfaces
UV and visible spectrum		Phototransformation may occur
Solubility in water at 20EC	pH mg/L 5 890 7 780	Very soluble at pH 5 and 7
Solubility (mg/L) in organic solvents	Solvent mg/L hexane 1.85 toluene 5.29 acetonitrile 57.0 ethyl acetate 28.0 1-octanol 1.43 methanol 22.9 acetone 62.4 methylene chloride 133.0	
n-Octanol–water partition coefficient (K_{ow})	pH K_{ow} 5 3.9 7 4.7	Will not bioconcentrate or bioaccumulate in biological tissue
Dissociation constant (pK_a)	$pK_a = 9.7 \pm 0.2$	Predominates in its neutral form at environmentally relevant acidic, neutral and basic pH; adsorption will not be significantly affected by differering soil or sediment pH
Stability (temperature, metal)	Stable for 14 days at 54EC Unstable in aqueous solution with iron metal or ferric ions	

End-use product: Curzate® 60 DF

Property	Result
Physical state	Solid granule
Formulation type	Wettable granule
Guarantee	60% cymoxanil, nominal

1.3 Classification and labelling

1.3.1 Cymoxanil DPX-T3217 (technical)

Technical cymoxanil was moderately toxic by the oral route, had low acute toxicity via the dermal and inhalation routes, was a minimal irritant to eyes and skin, and was not a skin sensitizer.

The proposed label should include the following statement to adequately identify the acute oral hazard.

Primary Display Panel: **WARNING POISON**.

1.3.2 Curzate® 60 DF (60% technical grade cymoxanil) end-use product

Curzate® 60 DF was highly toxic by the oral route and of low acute toxicity via the dermal and inhalation routes, a moderate irritant to eyes, slightly irritating to skin and not a skin sensitizer. None of the inert ingredients appear on the U.S. Environmental Protection Agency (EPA) lists of inerts of toxicological concern (all are on list 3 or 4B).

The proposed label should include the following statement to adequately identify the acute oral and eye irritation hazards.

Primary Display Panel: **DANGER POISON, Caution Eye Irritant**.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

A single high performance liquid chromatography (HPLC) method was used for the determination of both the active substance and the significant structurally related impurities (content $ 0.1%) in the technical product. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

An HPLC method was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy, and is suitable for use as an enforcement analytical method.

2.3 Methods for residue analysis

Multi-residue methods for residue analysis
Recoveries of cymoxanil in grapes ranged from 70 to 95% at spiking levels of 0.05 and 0.01 parts per million (ppm) using Protocol D.
Other protocols from existing multi-residue methods not found to be suitable for the determination of cymoxanil residues in potatoes.

Methods for residue analysis of plants and plant products
Data gathering method
HPLC method with UV detection (limit of quantitation (LOQ): 0.05 ppm; limit of detection (LOD): 0.02 ppm)

Residue of concern: Cymoxanil

Matrix	Tubers, white	Tubers, red	Flakes	Dried peels	Chips
Spiking levels (ppm)	0.05–0.33	0.05–0.30	0.05–0.30	0.05–0.30	0.05–0.30
Range of recoveries (%)	73–109 (n = 87)	75–98 (n = 3)	86–98 (n = 3)	77–90 (n = 3)	88–101 (n = 3)
Recovery mean (%) ± SD	88 ± 10.5	87 ± 11.5	92 ± 6.0	83 ± 6.6	93 ± 6.8

Confirmatory method
Liquid chromatography – mass spectrometry with selected ion monitoring
Recoveries ranged from 76–88% (average: 81 ± 5%; n = 9) at spiking levels of 0.02–0.10 ppm

Enforcement method
Enforcement method equivalent to data gathering method

Interlaboratory validation
Interlaboratory validation indicated good reliability and reproducibility

Analytical method: animal matrices
No analytical methods for animal matrices were submitted

3.0 Impact on human and animal health

3.1 Integrated toxicological summary (see Appendix I)

Cymoxanil (DPX-T3217) administered orally to rats was rapidly absorbed, and metabolised (hydrolysed) completely to methoximinoacetic acid and glycine, which was followed either by reincorporation in peptides or conjugation and elimination as hippuric acid and phenylaceturic acid. Only trace amounts were excreted unchanged in feces. Elimination occurred rapidly mainly via urine and partly via feces and expired air. Cymoxanil had limited tissue accumulation and highest tissue levels occurred in the liver,

kidney and skin. No sex differences in tissue distribution, metabolism or elimination were observed.

Technical cymoxanil was moderately toxic by the oral route and of low acute toxicity via the dermal and inhalation routes of exposure in rats. It was minimally irritating to the skin and eyes in rabbits, and not a dermal sensitizer in guinea pigs. Curzate® 60 DF was highly toxic by the oral route of exposure in rats and was of low acute toxicity via the dermal and inhalation routes of exposure in rats. It was a moderate irritant to rabbit eyes, slightly irritating to rabbit skin and was not a dermal sensitizer in guinea pigs.

In subchronic dietary repeat dosing studies conducted in mice, rats and dogs, the dog was identified as the most sensitive species with toxicity manifesting in hematological parameters at the lowest dose level. Similar effects were seen on hematological parameters in dogs following chronic exposure. Rats and mice on the other hand were able to tolerate greater (up to five fold) doses of cymoxanil than dogs; however, toxicity was more pronounced, with the liver, pancreas and spleen being target organs in mice, and toxicity of the hematological parameters and of the male reproductive system (testes and epididymis) occurring in rats at higher doses. No evidence of toxicity was observed in rats following dermal exposure at the limit dose of 1000 mg/kg body weight (bw)/day. Toxicity appeared to be cumulative in rats and mice where long-term exposure produced an increase in the incidence and severity of pathology at lower effect levels. No gender sensitivity was evident in any of the test species. Cymoxanil was not oncogenic in mice and rats. Although cymoxanil was positive in the in vitro chromosomal aberration assays in human lymphocytes and an unscheduled DNA synthesis assay in rat hepatocytes, negative findings were obtained in all the in vivo mutagenicity assays and in the carcinogenicity studies perfomed in rats and mice, indicating that cymoxanil was not genotoxic in vivo in mammals.

The male reproductive system was identified as the major target organ in rats where degenerative changes of the testes and epididymis occurred following subchronic and chronic dietary exposure. Decrease in the weights of the testes and epididymis and aspermatogenesis were reported in the 90-day feeding study in dogs, although these changes were absent in dogs following one-year dietary exposure at similar dose levels. Decrease in absolute testes weight was also noted in F_1 adult males in the two-generation rat reproductive toxicity study, and a decrease in the number of male pups per litter were observed in the rat developmental toxicity study. Cymoxanil did not affect fertility or reproductive performance in rats and it was not teratogenic in rats and rabbits. Although segmental delays in ossification of ribs and vertebrae occurred, no evidence of age-related sensitivity was observed, as effects in the offspring occurred only at or above maternally toxic doses in rats and rabbits. In view of the observed effects on the male to female ratio in pups, coupled with the observed effects on male reproductive system in all three species, submission of a dominant lethal study is advisable.

Cymoxanil also caused neurological signs and neuropathological lesions following long-term exposure in rats where retinal atrophy and sciatic nerve axonal – myelin

degeneration occurred in females and clinical signs of hyperactivity and aggressiveness were noted in males. No developmental anomalies of the nervous system, however, occurred in the developmental toxicity studies in rats and rabbits, and no behavioural or neurological effects were observed in the offspring in the two-generation reproductive-toxicity study. In addition, the neurological component of the combined 13-week subchronic-neurotoxicity study in rats demonstrated no effects on the functional observation battery or on motor activity.

Cymoxanil showed evidence in several studies of effects on different endocrine tissues (testes, thyroid an pancreas) in several different mammalian species. This coupled with a change in the male/female sex ratio in the development toxicity study in rats, and effects noted in a mallard duck and a northern bobwhite quail reproduction studies (see section 6.1) supports the potential for endocrine effects of cymoxanil.

3.2 Determination of acceptable daily intake

The recommended acceptable daily intake (ADI) for cymoxanil (DPX-T3217) is 0.01 mg/kg bw/day. The dog was identified as the most sensitive species where target organ toxicities were observed at a much lower dose levels when compared with rats and mice. The most appropriate study for selection of toxicity end points for dietary exposure was the one-year dietary study in dogs with a NOAEL of 3 mg/kg bw/day in males where decreases in red blood cell counts, hemoglobin, hematocrit and mean corpuscular hemoglobin concentration, as well as increased mean corpuscular volume were observed at 5.7 mg/kg bw/day.

A 3× safety factor (SF) additional to the usual 100-fold for inter- and intra- species variation was deemed necessary, owing to observed reproductive organ toxicity, neurological signs and neuronal lesions, coupled with the absence of a developmental neurotoxicity, as well as a dominant lethal study. Although no effects on fertility and reproductive perfomance were observed and the overall statistical analysis of the three rabbit developmental toxicity studies indicated no evidence of age related sensitivity, there may an indication of an age-related sensitivity in two out of three of these rabbit developmental toxicity studies. An SF of 300-fold, therefore, was applied to the NOAEL of 3 mg/kg bw/day as follows:

$$\text{ADI for cymoxamil (DPX-T3217)} = \frac{\text{NOAEL}}{\text{SF}} = \frac{3.0}{300} = 0.01 \text{ mg/kg bw/day}$$

This ADI provides margins of safety equal to or greater than 400 to the NOAEL for reproductive organ toxicity as well as for the neurological end points (lowest NOAEL = 4.08 mg/kg bw/day in the two-year dietary study in rats) and 2500-fold safety margin for the decreased number of male pups born per litter end point (NOAEL = 25 mg/kg bw/day in rat developmental study).

3.3 Acute reference dose

Acute toxicity females (13+)
On the basis of increased incidence of delayed ossification of the ribs and vertebrae observed in rat and rabbit teratogenicity studies following exposure to cymoxanil (effects observed at maternally toxic doses), an acute reference dose (ARfD) was deemed necessary for the subpopulation of females (13+).

An additional (3×) uncertainty factor (in addition to the 100-fold for inter- and intra-species variation) was recommended owing to (*a*) observed neurological signs and neuronal lesions, coupled with the absence of a developmental neurotoxicity and (*b*) a doubtful assessment of an age-related sensitivity in rabbit developmental studies where the overall statistical analysis of the three studies indicated no evidence of age-related sensitivity; however, two out of three of these studies individually may suggest otherwise. By applying an uncertainty factor of 300-fold to the NOAEL of 4 mg/kg bw/day in the rabbit teratogenicity study, therefore, an ARfD of 0.013 mg/kg bw/day was achieved.

Acute toxicity to the general population
An ARfD for the general population was not established, since there were no observable effects in oral toxicity studies and no maternal toxicity in developmental studies in rats and rabbits that were attributable to a single dose.

3.4 Toxicology end-point selection for occupational and bystander risk assessment

The end-use product, Curzate® 60 DF, has high toxicity by the oral route of exposure and low toxicity by the dermal and inhalation routes. It is moderately irritating to the eyes, slightly irritating to the skin and is not a dermal sensitizer in guinea pigs.

In repeat dose toxicology studies with cymoxanil, target organs were identified as the testes, epididymis and exocrine pancreas in rats and mice, the erythropoietic system in rats and dogs, and sciatic nerve and retina in rats. Cymoxanil is not considered genotoxic, oncogenic or teratogenic.

For farmers, custom applicators and scouts re-entering treated fields, the expected duration of exposure is short- to intermediate-term and predominantly via the dermal route. A comparison of toxicity following dosing by the oral route and the lack of systemic effect following dosing by the dermal route indicates low dermal absorption in rats. Although the dog was identified as the most sensitive species, toxic effects observed in the rat and the dog were similar. In the absence of a dermal absorption study, the 28-day dermal toxicity study in rats is considered most appropriate for occupational risk assessment. In this study, the NOAEL was 1000 mg/kg bw/day, the highest dose tested. A wide range of parameters were examined in this study, including clinical signs, body weight gain, hematology, clinical chemistry and macroscopic and microscopic pathology.

An additional three-fold safety factor, beyond the 100-fold to account for intra- and inter-species differences, is recommended owing to the observed reproductive organ toxicity and neurological signs and neuronal lesions in repeated-dose toxicology studies, coupled with the absence of dominant lethal and developmental neurotoxicity studies.

3.5 Impact on human health arising from exposure to the active substance or to impurities contained in it

3.5.1 Operator exposure assessment

Curzate® 60 DF would be applied to potatoes using groundboom equipment at an application rate of 135 g a.i./ha. It could be applied up to seven times per growing season, with five- to seven-day intervals between applications. Typically, application would start in early July and continue until harvest. Exposure to mixers, loaders and applicators would, therefore, be of short- to intermediate-term duration.

Mixer, loader and applicator exposure was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. The Pesticide Handlers Exposure Database is a compilation of generic mixer, loader and applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. The following PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. As exposure via the inhalation route was a minor component of overall exposure, exposure estimates were based on dermal deposition potential.

To estimate exposure for each use scenario, appropriate subsets of data were created from the mixer, loader and applicator database files of the PHED. All data were normalized for kilogram of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part is most appropriate to the distribution of data for that body part. Estimates were derived for individuals wearing one layer of clothing during mixing, loading and application, and gloves during mixing and loading.

Exposure for mixers, loaders and applicators was estimated to be 25 Fg a.i./kg bw/day for farmers and 154 Fg a.i./kg bw/day for custom applicators.

On the basis of these exposure estimates, the following margins of exposure were derived.

Occupational scenario	Exposure[1] (mg/kg bw/day)	Margin of exposure NOAEL (1000 mg/kg bw/day)[2]
Mixer, loader and applicator exposure[3]		
Farmer	0.025	40 000
Custom applicator	0.154	6500

1 On the basis of a 70-kg operator; typical North American use patterns of 65 ha/day (farmer) and 400 ha/day (custom applicator) for groundboom application; application rate of 135 g a.i./ha.
2 On the basis of a 28-day rat dermal study, highest dose tested.
3 Individuals wearing one layer of clothing during all activities, and gloves during mixing and loading.

These margins of exposure are considered adequate.

3.5.2 Bystanders

Given that application is restricted to agricultural areas, and that the product would be applied using ground equipment only, exposure and risk to bystanders is expected to be negligible.

3.5.3 Workers

Individuals would re-enter treated agricultural sites to carry out cultivation-related tasks that involve contact with treated foliage. The potential for re-entry exposure during harvesting is low. Potato harvesting is usually mechanical and harvesters generally wear long clothes, dust masks and gloves. As well, the proposed preharvest interval (PHI) is eight days. Potential exposure to scouts who re-enter the fields to look for signs of disease was considered to represent the highest exposure potential scenario for the proposed uses of Curzate® 60 DF.

As the applicant did not submit relevant data, a conservative Tier 1 exposure assessment was conducted. On the basis of the assumptions that scouts would spend four hours per day in potato fields, that all applied pesticide lands on the leaf surface, that 20% of this residue is dislodgeable, that there is no dissipation of residue over the time period of seven applications, and that applying a generic transfer coefficient of 1000 cm^2/h, the estimated mean dermal deposition is 61 Fg a.i./kg bw/day.

On the basis of the NOEL of 1000 mg/kg bw/day in the 28-day dermal toxicity study in rats, a margin of exposure of 16 000 is obtained for scouts. As this was considered to represent the highest potential exposure scenario for re-entry workers, margins of exposure for all post-application activities for proposed uses are considered adequate.

4.0 Integrated food residue chemistry summary

The plant and goat metabolism studies appeared to indicate that ^{14}C-cymoxanil was extensively metabolised, primarily to the amino acid glycine, which was subsequently degraded or reincorporated into other naturally occurring products.

On the basis of the similarity of the plant, goat and rat metabolic profiles, the residue of concern (ROC) was defined as cymoxanil.

The confined crop rotation study indicated that residues of cymoxanil were nondetectable (<LOD; 0.02 ppm) in all fractions of the rotational crops (wheat, sugarbeets and leaf lettuce) planted in soil that had been treated with cymoxanil at the rate of 1.21 kg a.i./ha (1.3× Canadian Good Agricultural Practices) and aged for 30 and 120 days. It appears unlikely, therefore, that residues of cymoxanil and its related metabolites in soil will translocate and bioaccumulate in the rotational crops.

An HPLC method with UV detection (254 nm) was used to quantitate residues of cymoxanil in potatoes and various other matrices. The method LOQ for cymoxanil was 0.05 ppm. Good linearity (correlation coefficient, $r > 0.9999$), was observed in the range of 0.02–0.30 ppm for cymoxanil. The interlaboratory validation did support the reliability and reproducibility of the Dupont method for the determination of cymoxanil residues in potatoes. The standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having good repeatability. Representative chromatograms of control samples showed no interferences from matrix components or from reagents, solvents and glassware.

The freezer storage stability study indicated that residues of cymoxanil were stable for 12.5 months when stored at –20ºC in potatoes. Plant metabolism and residue trial samples were analysed within 6.5 months. Residues of cymoxanil in the treated potato tuber samples, therefore, appeared stable when stored from the time of collection until analysis.

The results from the 19 U.S. and two Canadian supervised field trials demonstrated that maximum residues in potatoes, treated with Curzate® M-8 (8% a.i., wettable powder formulation of cymoxanil and mancozeb) at rates ranging from 1.21 to 6.05 kg a.i./ha (1.3–6.4× Canadian good agricultural practices) and harvested 0–14 days following the last application, did not exceed the LOQ (0.05 ppm). A maximum residue limit (MRL) of 0.05 ppm, therefore, should be established to cover residues of cymoxanil on potatoes.

None of the supervised field trials was conducted according to the proposed Canadian use pattern (0.135 kg a.i./ha, seven applications per season, maximum seasonal application rate of 0.945 kg a.i./ha per season, eight-day PHI), nor were any of the trials treated with the Curzate® 60 DF formulation, proposed for Canadian registration. The Pest Management Regulatory Agency, therefore, can only support a temporary registration pending the submission of a minimum of two side-by-side field trials in a major Canadian

potato growing region (1A, Atlantic or 5, Southern Ontario), demonstrating the equivalence between the Curzate® M-8 and Curzate® 60 DF formulations.

In the residue decline study, potatoes were treated with Curzate® M-8 at rates of 1.21 kg a.i./ha (1.3× good agricultural practices) and 2.42 kg a.i./ha (2.6× good agricultural practices) and harvested 0–28 days following the last application. Residues did not exceed 0.05 ppm (LOQ); therefore, the study supports the proposed eight-day PHI.

Because residues of cymoxanil were below the LOQ (<0.05 ppm) on potatoes treated at 6.4× the proposed Canadian application rate and harvested one day following the last application, a potato processing study was not required. As a result, residues of cymoxanil in potato processed fractions (flakes, peels and chips) will be covered under the raw agricultural commodity (RAC) MRL of 0.05 ppm.

No freezer storage stability study depicting the behaviour of cymoxanil residues in animal matrices was submitted with this petition; however, data from the lactating goat metabolism study indicated that the qualitative and quantitative nature of the residues in animal matrices did not change considerably during the storage period. In the event the petitioner requests an expansion of use for cymoxanil, a freezer storage stability study using spiked animal matrices should be submitted.

According to the supervised residue trials, residues of cymoxanil in livestock feed items (processed potato waste and potato culls) are unlikely to exceed the LOQ when treated according to the proposed Canadian use pattern. On the basis of the maximum anticipated theoretical dietary burdens of cymoxanil to beef and dairy cattle and the absence of quantifiable residues of cymoxanil or any compound of toxicological interest in milk, meat and meat by-products, as demonstrated in the goat metabolism study, an MRL of 0.05 ppm should be established to cover potential residues of cymoxanil in milk, meat and meat by-products of cattle, horses, hogs and sheep.

Because there are no poultry feed items associated with this petition, no data depicting the magnitude of cymoxanil residues in poultry commodities were required.

For the chronic dietary-risk assessment, the potential daily intake (PDI) was determined using the proposed MRLs on plant and animal commodities and the Dietary Exposure Evaluation Model™ (DEEM) software. The assessment was conducted using the 1994–1996 Continuing Survey of Food Intake for Individuals. The PDI accounted for 14 and 25% of the ADI (0.01 mg/kg bw/day) for the total population and children 1–6 years, respectively (including 10% allocation to water). For females of child-bearing age, an ARfD (0.01 mg/kg bw/day) was recommended. The acute dietary-risk assessment, conducted for this specific age group (female 13+, pregnant or nursing), indicated that the PDI represented 20% of the ARfD (95th percentile), while for children (1–6 years), the PDI represented 47% of the ARfD (95th percentile), the highest among all population subgroups, including the 10% allocation to water.

Consequently, the proposed domestic use of cymoxanil on potatoes does not pose an unacceptable dietary (both food and water) risk to any segment of the population, including infants, children and adults.

5.0 Fate and behaviour in the environment

5.1 Summary of the fate and behaviour of cymoxanil in the environment

5.1.1 Transformation

Cymoxanil is relatively unstable in the environment, except under conditions of low pH in aquatic solutions. Base-catalysed hydrolysis and biotransformation are the principal routes of transformation of cymoxanil in the environment. No major transformation products were detected in soil samples. The major transformation products that were detected in aqueous samples from laboratory studies were susceptible to biotransformation and did not continue to accumulate with time. Cymoxanil is nonpersistent in soil and water under environmentally relevant conditions. Data regarding transformation processes are summarized in Table 1 of Appendix III.

5.1.2 Mobility

Supplemental information from laboratory studies of mobility indicated that cymoxanil and its transformation products were poorly adsorbed to soils and may be mobile (Table 1, Appendix III). The results of the field studies, however, indicated that cymoxanil was not mobile below 15 cm in soils and, consequently, should not pose a risk of leaching to groundwater. The leaching potential for cymoxanil to contaminate groundwater was also investigated by using Cohen et al. (1984), the Ground Water Ubiquity Score (GUS) of Gustafson (1989), and the Expert System for Pesticide Regulatory Evaluation and Simulation (EXPRES) model. Cymoxanil satisfies four of the seven leaching criteria of Cohen et al. (1984), indicating that the leaching potential of cymoxanil is borderline. The calculated GUS of 1.5 falls into the range for nonleachers (<1.8). For EXPRES, two indices are calculated, leaching potential (LP) (a relative measure of the potential of the pesticide to leach to the water table) and leaching index (LI) (a relative measure of the potential migration distance of the pesticide) and compared with four pesticides known from field measurements to have leached to groundwater. The indices for cymoxanil are contradictory, ranking it as high for LP, but relatively low when considering the LI. The LI score considers a half-life in soil and is likely to be a better indicator of leaching for cymoxanil. Overall, cymoxanil should not, therefore, pose a risk of leaching to groundwater.

5.1.3 Transformation products

No major transformation products (>10% applied radioactivity), other than CO_2, were detected in soil samples from laboratory studies. Several minor transformaton products (<10% applied radioactivity) were detected in the study of phototransformation on soil,

but all were transient in nature. The principal route of transformation for these intermediate compounds may be microbially-mediated and, as indicated by the results of the submitted studies, proceeds quickly.

Major and minor transformation products were detected in aquatic laboratory studies (see Table 2, Appendix III). As hydrolysis of cymoxanil proceeds faster with increasing pH, the amount of accumulating transformation products also increased with pH. Transformation products were susceptible to biotransformation and, as a result, did not continue to accumulate over time.

5.2 Expected environmental concentrations

5.2.1 Soil

Cymoxanil is proposed for use in Canada on potatoes at a rate of 135 g a.i./ha, with applications a minimum of five to seven days apart, and no more than seven applications per season. The maximum cumulative application rate on soil, taking into account a soil decline time 50% (DT_{50}) of eight days for cymoxanil, is 366 g a.i./ha. Assuming a soil bulk density of 1.5 g/cm^3, application at the maximum cumulative rate (366 g a.i./ha) to bare soil with no interception by foliage, and uniform mixing in soil over a depth of 15 cm, the expected environmental concentration (EEC) of cymoxanil in soil is 0.163 mg a.i./kg soil dry weight.

5.2.2 Water

Expected environmental concentrations in water were calculated by assuming a worst-case scenario in which the Canadian label rate (135 g a.i./ha) was applied the maximum recommended number of times (seven) at the shortest interval allowed between sprays (five days). To calculate a maximum cumulative application rate, transformation of the parent compound in soil (runoff) and water (direct overspray) was taken into consideration.

Expected environmental concentrations in water from direct overspray
The maximum cumulative application to water owing to spray drift was 268 g a.i./ha. The concentration of cymoxanil resulting from a direct overspray of the proposed cumulative application rate of 268 g a.i./ha in a 30 cm depth of water is 0.0893 mg a.i./L. The same scenario and concentration is assumed for determining risk in estuarine and marine waters.

Expected environmental concentrations in pond water (shallow water) from runoff
Estimated seasonal losses from runoff following the application of Curzate® 60 DF Fungicide to soil would be expected to be 0.5% or less of the amount applied (Wauchope, 1978). Assuming a scenario in which a 100-ha watershed is treated with seven sequential applications of cymoxanil at the proposed Canadian label rate (100% deposition; equivalent to a cumulative rate of 366 g a.i./ha when considering the

half-life in soil), and 0.5% of the applied compound enters a one-hectare pond through runoff water, the EEC of cymoxanil in a 30 cm depth of pond water would be 0.061 mg a.i./L. The same scenario and concentration is assumed for determining the risk in estuarine and marine waters.

5.2.3 Vegetation

Concentrations of cymoxanil on vegetation were estimated using a nomogram developed by the EPA (Hoerger and Kenaga, 1972). A fresh weight to dry weight conversion was also calculated. A cumulative rate of 945 g a.i./ha was used, which assumed no transformation as the half-life of cymoxanil on vegetation is unknown. The EECs were used to estimate the highest concentration of cymoxanil that may be present in a typical diet of wild birds and some common mammals when exposed to maximum application rates and frequencies (see Table 3, Appendix III). These concentrations were used to determine the risk to wild birds and mammals.

6.0 Effects on nontarget species

6.1 Terrestrial species

Cymoxanil is practically nontoxic to birds and bees and is moderately to highly toxic to mammals on an acute basis. Cymoxanil was practically nontoxic to birds on a short-term dietary basis. Minimal effects were seen on the terrestrial vascular plants that were tested at 2 kg a.i./ha, on the basis of seedling emergence and vegetative vigour. In the reproduction study with northern bobwhite quail and mallard ducks, effects, such as hemorrhagic uterus, regressing and inactive ovaries and small testes were noted. There were also treatment-related reductions in the number of eggs laid, embryos, hatchlings and 14-day old survivors. In light of similar and other adverse effects on reproductive and other endocrine tissue in mammalian studies, this further supports the potential for endocrine effects on cymoxanil. Data are summarized in Appendix III, Table 4.

6.2 Aquatic species

Cymoxanil is slightly toxic to *Daphnia magna*, mysid shrimp, eastern oyster, bluegill sunfish, carp, rainbow trout and sheepshead minnow on an acute basis. Minimal effects were seen with *Selenastrum capricornutum*, *Skeletonema costatum* and *Lemna gibba*. In chronic studies (21–28 days), NOEC values for *Daphnia magna*, mysid shrimp and rainbow trout were 15 mg a.i./L, 1.70 mg a.i./L and 0.22 mg a.i./L, respectively. The NOEC values for longer-term studies with early life-stages of rainbow trout and sheepshead minnow were <0.031 mg a.i./L and 0.0942 mg a.i./L, respectively. The most sensitive end points for algae were for *Anabaena flos-aquae* (0.0652 mg a.i./L) and *Navicula pelliculosa* (0.0633 mg a.i./L). Data are summarized in Table 5 of Appendix III.

6.3 Environmental risk assessment

Risk quotients, using the estimated environmental concentrations and toxicity end points (NOEC), were used to determine the risk of cymoxanil to terrestrial and aquatic nontarget organisms (see Tables 6 and 7, Appendix III). Cymoxanil will not pose a risk to wild birds, wild mammals, earthworms, honeybees, terrestrial vascular plants, mysid shrimp, *Skeletonema costatum*, *Selenastrum capricornutum* or duckweed, and will not pose an acute risk to juveniles of bluegill sunfish, rainbow trout, carp and sheepshead minnow. Also, cymoxanil will not pose an acute risk to *Daphnia magna*.

Cymoxanil may pose a risk to early life-stages of rainbow trout and sheepshead minnow, to *Daphnia magna* (long-term exposure) and to the algae *Anabaena flos-aquae* and *Navicula pelliculosa*.

6.4 Mitigative measures

To mitigate the effects on nontarget aquatic species, buffer zones should be observed for aquatic habitats. Buffer zones are determined by using the most sensitive end point, from submitted toxicity studies, which represents the nontarget group at greatest risk. Curzate® 60 DF cannot be applied without Manzate® 200 DF (75% mancozeb). As mancozeb is highly toxic to nontarget aquatic organisms, the calculation of a buffer zone for this mandatory tankmix considers the toxicities of both active ingredients. A buffer zone of 50 m, therefore, is required between the downwind edge of the boom and sensitive aquatic habitats (freshwater and estuarine) such as ponds, lakes, rivers, streams and wetlands.

6.5 Outstanding data requirements and clarifications

- DACO 8.2.3.2 Hydrolysis
  The applicant should explain if other cleavage products could have been produced in the hydrolysis study, besides W3595, or if they would be structurally similar to other transformation products already identified.

- DACO 8.2.3.4.2 Aerobic soil
  Replicate A showed an increase in cymoxanil (% applied radioactivity) on day 6, instead of a decrease, from the previous sampling interval (from 24.4 to 73.6%). This was also the sample that showed a total recovery of 148% applied radioactivity. The applicant should explain the significance of this sudden increase in the concentration of cymoxanil in soil.

  The applicant should clarify a discrepancy, between Tables II and III in the study report, in the values of $^{14}CO_2$ from eight-hour sample replicates (A and B).

- DACO 8.2.3.5.2 Aerobic aquatic
  Clarification of the identity of the major transformation product, RF 1, should be provided, as well as a proposed pathway of aerobic aquatic biotransformation. The applicant should indicate if samples (water and extracts) were stored before analysis and, if so, for how long.

- DACO 8.2.3.5.6 Anaerobic aquatic
  Data regarding the storage stability of cymoxanil in frozen water and sediment should be reported. Rationale for combined analyses of compounds should be provided (e.g., M1, M2 and M3). The identity of transformation products M1a and M3a should also be provided.

- DACO 8.3.2.1 Canadian terrestrial field study
  The applicant should address the apparent instability of cymoxanil in samples from the field study. Recovery in time zero samples was low. Application rates were verified by measuring the time taken to apply the compound to the test plot. Another method should have been used to confirm the application rate.

6.6 References

Cohen, S.Z., S.M. Creeger, R.F. Carsel and C.G. Enfield. 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. pp. 297–325. *In* R.F. Krugger and J.N. Seiber, eds., *Treatment and Disposal of Pesticide Wastes*. ACS Symposium Series No. 259. American Chemical Society, Washington, D.C., pp. 297–325.

Gustafson, D.I. 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry, **8**: 339–357.

Wauchope, R.D. 1978. The pesticide content of surface water draining from agricultural fields — a review. Journal of Environmental Quality, **7:** 459–472.

7.0 Integrated efficacy summary

7.1 Effectiveness against late blight of potato caused by *Phytophthora infestans*

Bridging data

Although the application is to register Curzate® 60 DF, most of the data submitted were measures of efficacy of Curzate® M-8, a premix of two active ingredients, cymoxanil (8%) and mancozeb (64%), combined in a 1:8 ratio. The ratio between the two actives in Curzate® M-8 is equivalent to the ratio of active ingredients of the tankmix on the proposed label. Furthermore, the total amount of active ingredient applied in plots treated with Curzate® M-8 is also equivalent to the total active ingredient as proposed on the label for the Curzate® 60 DF – Manzate® 200 DF tankmix. The possibility, therefore, of using data with Curzate® M8 to support the claim with the Curzate® 60 DF – Manzate® 200 DF tankmix was considered.

Three trials were submitted where the efficacy of Curzate® M-8 and Curzate® 60 DF tankmixed with Manzate® 200 DF were compared. However, the amount of active ingredient applied in plots treated with the tankmix was higher than in plots treated with Curzate® M-8. The ratio of the two active ingredients (cymoxanil and mancozeb) in Curzate® M-8 is 1:8, while it varied from 1:11 to 1:15 in the tested tankmix. The submitted bridging data are not appropriate and efficacy data with Curzate® M-8 cannot be used to support the use of the Curzate®–Manzate® tankmix at the rates proposed on the label.

Efficacy data

Seven trials were submitted where the efficacy of cymoxanil was tested in tankmix with mancozeb. The distribution of the trials, conducted in 1997, is British Columbia, 1; Manitoba, 1; Quebec, 1; Prince Edward Island, 1; North Dakota, 1; Pennsylvania, 1; and Oregon, 1.

Various combinations of cymoxanil and mancozeb were applied in season-long programs alone, or in alternation with mancozeb. No efficacy data, however, with the rates proposed on the label were submitted. Regardless of the total amount of active ingredient in the mix or the ratio between the two actives, all treatments significantly controlled late blight infections compared with the untreated controls (89%, overall average, 16 data). Furthermore, the performance of the various tankmixes was comparable to the performance of commercial standards (chlorothalonil, mancozeb, or mancozeb and dimethomorph).

Similar results were reported in literature. Combinations of cymoxanil and mancozeb were very effective in controlling late blight of potato; however, all the rates tested were above the rates on the proposed label. A tankmix of 139 g a.i./ha of cymoxanil and 1470 g a.i./ha of mancozeb provided 95% control (average of three trials) (Inglis et al., 1998; James and Stevenson, 1998; Ludy and Powelson, 1998). Lower amounts of mancozeb (1269 or 987 g a.i./ha) in combination with various rates of cymoxanil (108, 121 or 141 g a.i./ha) also provided significant control (85% average), comparable to commercial standards (Christ et al., 1998; Kirk et al., 1998).

With lower rates of mancozeb (1.26 and 1.47 kg/ha), efficacy improved with the higher rates of cymoxanil (120 and 140 g a.i./ha) in the tankmix. One trial compared 1.26 or 1.47 kg mancozeb and 140 g of cymoxanil in tankmixes and showed the same level of disease control for both tankmixes.

These data support the use of the cymoxanil in tankmix with mancozeb for the control of late blight of potato (*Phythopthtora infestans*), as defined on the proposed label, at the rate of 0.225 kg product/ha (0.135 kg a.i./ha) of Curzate® 60 DF tank-mixed with 1.6 kg product/ha (1.2 kg a.i./ha) of Manzate® 200 DF.

When currently registered products containing mancozeb as the only active ingredient are used, the recommended amount of mancozeb is 0.825–1.69 kg/ha, with the lowest rate applied when plants are 10–15 cm high. The rate is then increased as foliage develops to the maximum, which is applied at row closure. The submitted data support rates of

mancozeb in the proposed tankmix of 1.2 kg a.i./ha, higher than the lowest registered rate (0.825 kg a.i./ha). Rates lower than the supported would probably adequately control late blight in potato plants before row closure; however, no data were submitted in this regard.

7.2 Integrated pest managment and the development of fungicide resistance

Cymoxanil inhibits nucleic acid synthesis in *Phytophthora infestans*. No shift in sensitivity has yet been detected in Europe, where cymoxanil has been registered for several years. The presence of sexual reproduction for *P. infestans* has been confirmed in Canada. The addition of the sexual cycle to a very efficient and effective asexual cycle increases the genetic flexibility and adaptation potential of this pathogen. The following application stategy is needed to reduce the potential for resistance build-up. Curzate® 60 DF is to be applied only in a tankmix with Manzate® 200 DF, a multisite inhibitor, and in alternation with other fungicides as a resistance management tool in a planned disease control program.

8.0 Toxic substance management policy

During the review of Cymoxanil Technical and Curzate® 60 DF, the PMRA has considered the implications of the federal Toxic Substances Management Policy (TSMP) and the PMRA Regulatory Directive DIR99-03 (*The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*) and has concluded the following:

- cymoxanil does not meet the criteria for persistence. Its values for half-lives in water (4–5 days), soil (6–8 days) and sediment (4–5 days) are below the TSMP Track-1 cut-off criteria for water ($182 days), soil ($182 days) and sediment ($365 days). Although a half-life in air was not submitted, cymoxanil is nonvolatile from moist soil and water surfaces.

- cymoxanil will not bioaccumulate. Studies have shown that the octanol–water partition coefficient is 0.7, which is below the TSMP Track-1 cut-off criterion of $5.0. Neither the bioaccumulation factor or the bioconcentration factor were reported.

- the toxicology of cymoxanil is described in detail in sections 3 to 6 of this document.

- cymoxanil does not contain any by-products or microcontaminants and does not form any degradation products that meet the TSMP Track-1 criteria. Impurities of toxicological concerns are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

9.0 Regulatory decision

Cymoxanil has been granted a temporary registration for use on potatoes, pursuant to Section 17 of the Pest Control Product Regulations, subject to the generation of the following studies and clarifications:

- a storage stability study
- three additional efficacy trials conducted at good agricultural practices and comparing the original proposed rate and the accepted rate for the tankmix to Curzate® M-8
- two side-by-side residue field trials demonstrating the equivalency of the Curzate® M-8 and Curzate® 60 DF formulations conducted in zones 1A and 5
- dominant lethal and developmental neurotoxicity studies
- clarifications on the following environmental studies

  DACO 8.2.3.2 Hydrolysis
  DACO 8.2.3.4.2 Aerobic soil
  DACO 8.2.3.5.2 Aerobic aquatic
  DACO 8.2.3.5.6 Anaerobic aquatic
  DACO 8.3.2.1 Canadian terrestrial field study

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
d	day
DEEM	Dietary Exposure Evaluation Model™
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EEC	expected environmental concentration
EPA	Environmental Protection Agency (U.S.)
EXPRES	Expert System for Pesticide Regulatory Evaluation and Simulation
GUS	Ground Water Ubiquity Score
h	hour
HGPRT	hypoxantine-guanine phosphoribosyl transferase
HPLC	high performance liquid chromatography
K_{ow}	octanol–water partition coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LI	leaching index
LOD	limit of detection
LOQ	limit of quantitation
LP	leaching potential
MAS	maximum average score
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MIS	maximum irritation score
MRL	maximum residue limit
NOAEL	no observable adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect limit
NZW	New Zealand white
PDI	potential daily intake
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodity
ROC	residue of concern
SF	safety factor
U.S.	United States

Appendix I Summary table of toxicology studies on cymoxanil

Metabolism			
Absorption: Readily and extensively absorbed. Distribution: Less than 1% in tissues after 96 h. The highest tissue levels occurred in liver, kidney and skin. Metabolism: Metabolised completely to methoximinoacetic acid (6.5–35%) and glycine (36.5–55%), which was either reincorporated in peptides or conjugated and eliminated as hippuric acid and phenylaceturic acid. Excretion: Rapidly and almost completely eliminated within 96 h. Excretion occured mostly through urine (64–75%), but also in feces (16–24%) and expired air (5%). Only trace amounts (<1%) were excreted unchanged in feces. Cymoxanil had limited bio-accumulation, and no sex difference in tissue distribution, metabolism or bio-elimination.			
Study	**Species (strain) and doses**	**LD_{50} (mg/kg bw) or LC_{50} (mg/L)**	**Significant effects and comments**
Acute studies: Technical			
Oral	Rats (Crl:CD® BR) 10/sex/dose 250, 500, 1000, 2000 or 3000 mg/kg bw	LD_{50} = 760 male, 1200 female, 960 (male and female)	MODERATELY TOXIC Clinical signs included lethargy, hunched or low posture, nasal and ocular discharge. Reversible after 2–3 days.
Dermal	Rabbits (NZW) 5/sex 2000 mg/kg bw (limit test)	LD_{50} > 2000 (male and female)	LOW TOXICITY No mortality. Slight erythema noted in one male.
Inhalation	Rats (Crl:CD® BR) 5/sex/dose 3.21, 4.98 or 5.06 mg/L for four hours	LC_{50} > 5.06 (male and female)	LOW TOXICITY Death of one male. Clinical signs included occular, nasal and oral discharge, low carriage, hunched posture, vocalisation, lethargy and abnormal morbility.
Dermal irritation	Rabbits (NZW) 4 males, 2 females, 0.5 g	Maximum average score (MAS) = 0.29	MINIMALLY IRRITATING
Eye irritation	Rabbits (NZW) 6 males, 18 mg (0.1 mL)	Maximum irritation score (MIS) = 0.5 at 24 h	MINIMALLY IRRITATING Mild conjuctival redness persisted in some beyond 24 h but dissappeared by 48 h.
Skin sensitization (Maximization test)	Guinea pigs (D/Hartley) 0.1 mL (3.0%) induction, 25% challenge	No sensitization	NOT A DERMAL SENSITIZER
Acute studies: Curzate® 60 DF (EUP)			
Oral	Rats (Crl:CD® BR) 10/sex/dose 241, 347 or 500 mg/kg bw	LD_{50} = 418 male, 467 female, 433 (male and female)	HIGHLY TOXIC Clinical signs included hypoactivity, tremors, ataxia, occular discharge, impaired righting reflex, vocalisation, emaciation, lethargy, prostration and convulsions. Signs in most resolved four days after dosing.

Study	Species (strain) and doses	LD_{50} (mg/kg bw) or LC_{50} (mg/L)	Significant effects and comments
Dermal	Rats (Crl:CD® BR) 5/sex 5000 mg/kg bw	LD_{50} > 5000 (male and female)	LOW TOXICITY No mortality and no clinical or other evidence of toxicity.
Inhalation	Rats (Crl:CD® BR) 5/sex 5.0 mg/L for four hours	LC_{50} > 5.0 (male and female)	LOW TOXICITY No mortality. Clinical signs included nasal discharge, dyspnea, weakness, gasping and lung sounds during dosing and nasal discharge and alopecia during recovery.
Skin irritation	Rabbits (NZW) 4 males, 2 females, 0.5 g in 0.2 mL water	MAS_{72h} = 0.75	SLIGHTLY IRRITATING Slight erythema in all, edema noted in one, erythema persisted in one case up to 72 h, irritation subsided in all by day 4.
Eye irritation	Rabbits (NZW) 6 males, 31 mg	MIS at 1 h = 7/110, persisted in 2/6 up to 72 h	MODERATELY IRRITATING (as per Kay and Calandra [1962]) Conjunctival redness, chemosis and discharge in most, iris effects in some. Irritation persisted in a few up to 72 h.
Skin sensitization (Buehler method)	Guinea pigs (Dunkin - Hartley) 20 males, 0.5 g in 0.5 mL for induction and challenge)	No evidence of sensitization	NOT A DERMAL SENSITIZER
Short term			
Study	**Species (strain)/doses**	**NOAEL/LOAEL (mg/kg bw/day)**	**Significant effects at different doses (mg/kg/bw/day)/Comments**
90-d dietary	Mice (CD1) 10/sex/dose 0, 50, 500, 1750, 3500 or 7000 ppm (0, 8.25, 82.4, 294, 566 or 1306, and 0, 11.3, 121, 433, 846 or 1130 mg/kg bw/day in males and females, respectively)	NOAEL = 8.25 male and 121 female LOAEL = 82.4 male and 433 female	$82.4: decreased body weight gain in males $294 male and 433 female: decreased body weight gain $566 male and 846 female: increased liver weight, increased spleen weight. in females 1306 male and 1130 female: terminated after three weeks owing to severe morbidity and mortality (with pancreatic necrosis and cerebral hemorhage)

Study	Species (strain)/doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg/bw/day)/Comments
90-d dietary (subchronic or neurotoxicity)	Rat (Crl:CD® BR) 10/sex/dose 0, 100, 750, 1500 or 3000 ppm (0, 6.54, 47.6, 102 or 224 and 0, 8, 59.9, 137 or 333 mg/kg bw/day for males and females, respectively)	Systemic toxicity NOAEL = 47.6 male and 59.9 female LOAEL = 102 male and 137 female Neurotoxicity NOAEL = 224 male and 333 female (highest dose tested)	$102 male and 137 female: decreased food efficiency (female), decreased lymphocyte and monocyte counts, and histopathology of testes and epididymis in males 224 male and 333 female: decreased body weight, decreased body weight gain No effects on functional observational battery or neuropathology
28-d dermal	Rats (Crl:CD® BR) 10/sex/dose 0, 50, 500 or 1000 mg/kg bw/day, six hours per day	NOAEL = 1000 (male and female) LOAEL > 1000	1000: no irritation and no systemic toxicity at highest dose tested (limit test)
90-d dietary	Dog, beagle 4/sex/dose 0, 100, 200 and 250 or 500 ppm (0, 3, 5, 5/11 mg/kg bw/day)	NOAEL not determined LOAEL = 3	$3: decreased body weight gain, decreased food consumption, decreased food efficiency in females, decreased red cell counts, hemoglobin and hematocrit in males $5: decreased red blood cell counts, hemoglobin and hematocrit (female) 5/11: decreased body weight, body weight gain and food efficiency, diarrhea, dermal atonia, decreased testes and epididymis weight and aspermatogenesis in males, one death, decreased kidney, liver and thyroid weight in females, altered clinical chemistry parameters in both sexes
12-month dietary	Dog, beagle 4/sex/dose 0, 25, 50 or 100 ppm (0, 0.7, 1.6 or 3.1 mg/kg bw/day) in females, and 0, 50, 100 or 200 ppm (0, 1.8, 3.0 or 5.7 mg/kg bw/day) in males	NOAEL = 3.1 female and 3 male LOAEL = 5.7 male and >3.1 female	5.7 male: decreased red blood cell counts, decreased hemoglobin, decreased hematocrit, decreased MCHC, increased MCV

Study	Species (strain)/doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg/bw/day)/Comments
Chronic toxicity and oncogenicity			
18-month dietary	Mouse (CD1) 80/sex/dose 0, 30, 300, 1500 or 3000 ppm (0, 4.19, 42, 216 or 446 mg/kg bw/day in males and 0, 5.83, 58.1, 298 or 582 mg/kg bw/day in females)	NOAEL = 4.19 male and 5.83 female LOAEL = 42 male and 58.1 female	$42 male and 58.1 female: decreased testes weight, increased incidence of degenerative changes of the testes and epididymal in males, gastroenteropathies in females, and hepatic lesions (apoptosis) in males and females >216 male and 298 female: decreased body weight, decreased body weight gain 446 male and 582 female: clinical signs (pallor, weakness, hunched posture), bone marrow congestion, decreased erythrocyte mass in males, increased mortality (with pancreatic necrosis) in females No carcinogenic effect in mice
Two-year dietary	Rat (Crl:CD® BR) 60–62/sex/dose 0, 50, 100, 700 or 2000 ppm (0, 1.98, 4.08, 30.3 or 90.1 and 0, 2.71, 5.36, 38.4 or 126 mg/kg bw/day in males and females, respectively)	NOAEL = 4.08 male and 5.36 female LOAEL = 30.3 male and 38.4 female	$30.3 male and 38.4 female: decreased body weight, decreased body weight gain, decreased food efficiency, aggressiveness and hyperactivity, epididymal changes, spermatid degeneration (males), retinal atrophy, liver histopathology and sciatic nerve atrophy (38.4 female only) 90.1 male and 126 female: increased incidence lung granulomas in males and lesions in lungs, pancreas and intestines and decreased food efficiency in females Not carcinogenic in rats

Study	Species (strain)/doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg/bw/day)/Comments
Reproduction and developmental toxicity			
Multigeneration	Rats (Crl:CD® BR), two-generations (one and two litters per generation) 30/sex/dose 0, 100, 500 or 1500 ppm via diet (0, 6.95, 34.75 or 111.95 and 0, 7.4, 38.1 or 119.6 mg/kg bw/day in males and females, respectively)	Systemic toxicity NOAEL = 6.95 male and 7.4 female LOAEL = 34.75 male and 38.1 female Offspring toxicity NOAEL = 7.4 LOAEL = 38.1 Reproductive toxicity NOAEL = 119.6 (the highest dose tested)	Parents $34.75 male and 38.1 female: decreased parental body weight (P_1 male, F_1 female), decreased body weight gain,decreased food consumption (P_1 [male]) 111.95 male and 119.6 female: decreased parental body weight (P_1 F_1), decreased body weight gain, decreased food consumption [P_1 (male), F_1 (male and female)], decreased food efficiency [P_1 (male and female)], clinical signs [missing tails, tails with necrotic tips, sores, stained fur, unspecified palpable masses likely due to mastitis (F_1)], decreased testes weight (F_1), death (owing to mastistis) of seven dams during resting phase between F_2 litters Offspring $38.1: decreased viability days 1–4 (F_1), decreased pup weight (F_{2b}) 119.6: clinical signs [gasping, no milk spots, subcutaneous hemorrhage, weakness (F_1 pups), stained perineum (F_{2a} and F_{2b} pups) and subcutaneous hemorrhages], decreased litter survival, decreased males alive on days 4–21 (F_1), decreased pup weight [F_1 + F_2 (male and female)], decreased testes weight (F_1) Reproductive parameters: No toxicity noted
Teratogenicity	Rats (Crl:CD® BR) 25 females/dose 0, 10, 25, 75, 150 mg/kg bw/day, by gavage (in methyl cellulose) on gestation days 7–16	Maternal NOAEL = 10 Maternal LOAEL = 25 Developmental NOAEL = 10 Developmental LOAEL = 25	Maternal toxicity $25: decreased body weight, decreased body weight gain, decreased feed consumption, alopecia Fetal toxicity $25: increased incidence of ossification delays $75: decreased mean number of male pups born per litter 150: increased resorptions per litter, decreased live fetuses per litter, decreased fetal weight Not teratogenic

Study	Species (strain)/doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg/bw/day)/Comments
Teratogenicity	Rabbits (NZW) 15/dose 0, 4, 8 or 16 mg/kg bw/day by gavage (in methyl cellulose) on gestation days 6–18	Overall (trend analysis) Maternal NOAEL = 4 Maternal LOAEL = 8 Developmental NOAEL = 4 Developmental LOAEL = 8	At all dose levels No maternal toxicity No fetal toxicity Not teratogenic
Teratogenicity	Rabbits (NZW) 15/dose 0, 8, 16 or 32 mg/kg bw/day by gavage (in methyl cellulose) on gestation days 6–18		Maternal toxicity $16: clinical signs (cold ears, anorexia and reduced fecal output), decreased body weight Fetal toxicity >8: increased incidence of delayed ossification of rib and vertebral skeleton Supplemental study, uncertainty regarding the animal source
Teratogenicity	Rabbits (NZW) 17–20/dose 0, 1, 4, 8 or 32 mg/kg bw/day by gavage (corn oil)		Maternal toxicity $ 8: increased maternal weight gain (post-dosing) Fetal toxicity $8: increased incidence of delayed ossification of rib and vertebral skeleton 32: cleft palate in two fetuses
Neurotoxicity			
Subchronic neurotoxicity	Rat (Crl:CD® BR) 10/sex/dose 0, 100, 750, 1500 or 3000 ppm (0, 6.54, 47.6 102 or 224 and 0, 8.0, 59.9, 137 or 333 mg/kg bw/day for males and females, respectively) for 90 days	NOAEL = 224 male and 333 female (the highest dose tested)	No effects on functional observation battery nor neuropathology at highest dose tested

Study	Species (strain) or cell type	Doses employed	Significant effects and comments
Genotoxicity			
Ames assay, point mutation	*S. typhimurium*, Salmonella four strains	10–2500 Fg/mL ± S9 fraction	Not mutagenic Cytotoxicity at $750 Fg/mL (–S9) and at $1000 Fg/mL (+S9)
Mammalian cytogenetics (in vitro)	CHO/HGPRT	0.005–0.75Fg/mL – S9, 0.01–1.5Fg/mL + S9	Not mutagenic
Mammalian chromosomal aberration (in vitro)	Human peripheral lymphocytes	0.1–1.5 mg/mL ± S9 activation	Positive at $0.85 mg/mL ± S9 activation Positive, clastogenic effect in vitro
Micronucleus assay (in vivo)	Mouse (Crl CD-1)	0, 125, 225, 450 mg/kg bw in males, 125, 225, 350 mg/kg bw in females, by gavage	Negative for micro nuclei Not genotoxic in vivo
In vitro unscheduled DNA synthesis	Rat (Crl CD-BR) primary hepatocytes	5–2000 0.75 Fg/mL	Positive from 5 to 500 Fg/mL, cytotoxicity at $750 Fg/mL Positive UDS in vitro
UDS ex vivo DNA damage and repair	Rats (Crl CD-BR) hepatocytes and spermatocytes	500 or 1000 mg/kg bw by gavage	Not genotoxic in cultured hepatocytes and spermatocytes of rats exposed ex vivo

Appendix II Residues

Table 1 Plant Metabolism

Cymoxanil readily metabolized in potatoes. No cymoxanil or structurally related metabolites detected in tuber samples. Radioactivity appears to be associated with glycine and incorporated into starch. Residue of concern (ROC) defined as the parent cymoxanil.		
Matrix	**PHI (days)**	**[2-^{14}C]cymoxanil label, TRRs (ppm)**
Potato tuber	10, 11	1.35–1.53; 2.20–2.51

Table 2 Confined Crop Rotation Studies

1.21 kg a.i./ha (1.3× good agricultural practices) soil application			
Crop	**Crop fraction**	**^{14}C-cymoxanil equivalent residues (ppm)**	
		Planting interval (days after treatment)	
		30 days	**120 days**
Winter	Forage	0.07	0.01
	Straw	0.14	0.12
	Grain	0.04	0.05
Sugarbeet	Foliage	0.02	<0.01
	Roots	0.01	<0.01
Leaf lettuce	foliage	<0.01	0.01

Table 3 Freezer Storage Stability Tests

Stability of cymoxanil residues in potato tubers at –20EC (10.5 and 12.5 months). Plant metabolism and residue samples were stored within the time periods studied.				
Storage interval (months)	**Spiking level (ppm)**	**Freshly spiked % residues recovered**	**Stored spiked % residues recovered**	**Corrected recovery in stored samples (%)**
0	0.25	72, 88 (80)	84, 88	—
10.5	0.25	88, 96 (92)	92, 108	100, 117
12.5	0.25	72, 80 (76)	80, 88	105, 116

Table 4 Animal Metabolism

In the goat metabolism study, no cymoxanil or related metabolites were detected in any matrices. Cymoxanil was extensively metabolised to the amino acid glycine, which was subsequently degraded or incorporated into other naturally occurring products. Excretion was rapid and occurred mostly through urine, but also in feces.
Because there are no poultry feed items associated with this petition, no data depicting the nature of cymoxanil residues in poultry commodities were required.
Residue of concern (ROC) defined as the parent cymoxanil.

Matrix	% of administered dose (ppm)
Tissues	3.66 (2.59)
Milk	2.64 (1.47)
Feces	18.30
Urine	23.60

Table 5 Cattle Feeding Study

Petitioner requested a waiver from the requirements for a cattle feeding study. The maximum anticipated dietary burdens of cymoxanil to beef and dairy cattle are 0.3 and 0.2 ppm, respectively, on the basis of diets consisting of processed potato waste and potato culls and the recommended MRL of 0.05 ppm. On the basis of the supervised field trials, residues of cymoxanil in potato tubers did not exceed the method LOQ (0.05 ppm), when treated at rates of up to 6.4× the proposed Canadian maximum seasonal application rate. The lactating goat metabolism study demonstrated that there were no residues of cymoxanil or any compound of toxicological interest detected at levels greater than 0.01 ppm in the milk, meat and meat by-products, when administered a diet representing 33–50× the theoretical maximum dietary burden. Since it appears unlikely that any residues of cymoxanil will bioaccumulate in milk, meat and meat by-products, no cattle feeding study was required.

Table 6 Hen Feeding Study

Because there are no poultry feed items associated with this petition, no data depicting the magnitude of cymoxanil residues in poultry commodities were required.

Table 7 Number of Field Trials by Region

Zones	1	0.042	3	5	0.2083	5B	0.3	9	10	11	12	14	Total
Required	3	4	—	3	1	1	1	—	—	—	1	2	16
Submitted	5	1 Can.	1	5	1 Can.	—	—	1	1	6	—	—	19 U.S. 2 Can.

Table 8 Supervised Residue Trials on Potato Tubers

Commodity and portion analysed	Formulation	Application			PHI (days)	Residues (ppm)
		No.	Total rate (kg a.i./ha)	% good agricultural practices		
U.S. trials						
Potato tubers	Curzate® M-8	9	1.21	130	0, 3, 5, 7, 8	<0.05
	Curzate® M-8	9	2.42	260	0, 3, 5, 7, 8	<0.05
	Curzate® M-8	9	6.05	640	1	<0.05
Canadian trials						
Potato tubers	Curzate® M-8	11	1.221	130	8, 14	<0.05

Table 9 Processing Studies

The petitioner requested a waiver from the requirements for data for processed potato commodities. As residues in potato tubers, grown in the United States, treated with cymoxanil at 1.3–6.4× the proposed Canadian maximum seasonal application rate (0.945 kg a.i./ha), did not exceed the method LOQ (0.05 ppm), a potato processing study was not required to support this petition.

Chronic dietary risk assessment using DEEM software on the basis of the 1994–1996 Continuing Survey of Food Intake by Individuals
ADI = 0.01 mg/kg bw; Tier I: using the proposed MRLs and 10% allocation to water

	All U.S. populations	All infants (<1 year)	Children (1–6 years)	Children (7–12 years)	Children (13–19 years)	Children (20+ years)	Seniors 55+
% of ADI	14	17	25	18	15	13	13

Acute dietary risk assessment using DEEM software on the basis of the 1994–1996 Continuing Survey of Food Intake by Individuals
ARfD = 0.01 mg/kg bw for females 13+; using the proposed MRLs and 10% allocation to water

99.9th percentile	Females 13+, pregnant and nursing	Children (1–6 years)
% of ARfD	20	47

Table 10 Proposed MRLs

Commodity	Proposed Canadian MRLs (ppm)	U.S. tolerances (ppm)
Potato tuber	0.05	0.05
Milk	0.05	Exempt
Meat and meat by-products of cattle, goat, hogs, horses, sheep	0.05	Exempt

Appendix III Environmental Tables

Table 1 Summary of transformation and mobility data for cymoxanil

Title	Value	Comments
Soil: cymoxanil technical		
Phototransformation on soil	$t_{½}$ = 15 days (continuous light) $t_{½}$ = 74 days (extrapolated to natural sunlight)	Not an important route of transformation (pH 6.4)
Aerobic soil biotransformation	DT_{50} = ~1 day DT_{90} = 9–19 days	Important route of transformation Non-persistent in soil (pH 6.4)
Mobility	Studies were not acceptable.	Supplementary information indicated that cymoxanil and transformation products are weakly adsorbed to soils and could be mobile.
Soil: Curzate® M-8 Fungicide (EUP)		
Canadian field dissipation (Nova Scotia and Manitoba)	DT_{50} = 5.7–8.0 days DT_{90} < 60 days	Non-persistent Cymoxanil is not mobile (pH 5.6 and ph 6.4).
U.S. field dissipation	DT_{50} < 1 to 8.7 days	Non-persistent Cymoxanil is not mobile (pH 6.3 and pH 7.8).
Water: cymoxanil technical		
Hydrolysis	$t_{½}$ = 148 days, pH 5 $t_{½}$ = 34 h, pH 7 $t_{½}$ = 31 min, pH 9	Important route of transformation Cymoxanil is hydrolytically unstable at higher pH.
Phototransformation in water	irradiated, $t_{½}$ = 1.7 days dark, $t_{½}$ = 147.5 days	Route of transformation (pH 5)
Aerobic water and sediment biotransformaton	DT_{50} = 4–5 days DT_{90} = 20–50 days	Important route of transformation Non-persistent (pH 7.1–pH 8.6)
Anaerobic sediment and water biotransformation	DT_{50} = 1.6 h DT_{90} < 1 day	Important route of transformation Non-persistent (pH 6.2–pH 7.8)

Table 2 Transformation products of cymoxanil and maximum amounts detected during the study (% applied radioactivity)

Transformation product	Phototransformation		Hydrolysis	Biotransformation		
	Soil	Aquatic		Soil	Aquatic	
				Aerobic	Aerobic	Anaerobic
2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide (“Z” configuration) (Q8761)	minor	n/d	n/d	n/d	n/d	n/d
oxamic acid, aminooxacetic acid (18474)	minor	minor	minor	n/d	minor	n/d
3-ethyl-4-(methoxyamino)-2,5-dioxo-4-imidazolidinecarbonitrile (JX915)	<11%; transient	52%	minor	n/d	n/d	minor
cyano(methyoxyimino) acetic acid (W3595)	minor	n/d	39% (pH 9)	n/d	n/d	minor

Transformation product	Phototransformation		Hydrolysis	Biotransformation		
	Soil	Aquatic		Soil	Aquatic	
				Aerobic	Aerobic	Anaerobic
1-ethyldihydro-6-imino-2,3,5(3*H*)-pyrimidinetrione-5-(*O*-methyloxime) (U3204)	minor	minor	60% (pH 9)	n/d	minor	n/d
ethylimidazolidinetrione (T4226)	minor	minor	n/d	n/d	minor	n/d
[[(ethylamino)carbonyl]amino]oxoacetic acid (KP533)	minor	minor	57% (pH 7)	n/d	n/d	minor
3-ethyl-4-(methoxyamino)2,5-dioxo-4-imidazolidinecarboxamide (KQ960)	minor	n/d	minor	n/d	n/d	n/d
ethylimidazolidinetrione-5-(*O*-methyloxime) (R3273)	minor	35%	10% (pH 7)	n/d	minor	n/d
Met (unknown)	n/d	n/d	minor	n/d	n/d	n/d
oxalic acid	n/d	n/d	minor	n/d	n/d	n/d
M1a, M1b, M1c, M1d, M1e, M3a	n/d	n/d	n/d	n/d	n/d	M1a, 28%
RF 1, 2, 3, 5, 7	n/d	n/d	n/d	n/d	RF 1, 69%	n/d
Polars and others	minor	n/d	minor	minor	minor	minor
CO_2	14%	not collected	not collected	64%	82%	35%

Note: All minor transformation products were <10% applied radioactivity; n/d = not detected.

Table 3 EECs (mg a.i./kg dw) of cymoxanil in the diet of wild birds and mammals after application at a cumulative rate of 366 g a.i./ha (assumes transformation equivalent to half-life on soil) and 945 g a.i./ha (no transformation)

Organism	Food item	% of diet	EEC 366 g a.i./ha			EECs in diet at 945 g a.i./ha		
			Food type	Each	Total	Food type	Each	Total
Bobwhite quail	small insects forage crops grain	30 15 55	72.3 102.8 12.4	21.7 15.4 6.8	43.9	186.7 265.4 32.0	56.0 39.8 17.6	113.4
Mallard	large arthropods grain	30 70	12.4 12.4	3.7 8.7	12.4	32.0 32.0	9.6 22.4	32
Mouse	short grass grain or seeds leaves or leafy crops	25 50 25	258.5 12.4 450.9	64.6 6.2 112.7	183.5	667.4 32.0 1164.2	166.8 16.0 291.1	473.9
Rat	short grass grain or seeds large insects	70 20 10	258.5 12.4 12.4	180.9 2.5 1.2	184.7	667.4 32.0 32.0	467.2 6.4 3.2	476.8

Table 4 Summary of effects of cymoxanil on terrestrial nontarget species

Organism	Organism and study	NOEC or NOEL	LC_{50} or LD_{50}	Interpretation
Birds	bobwhite quail; acute oral	175 mg a.i./kg bw	>2250 mg a.i./kg bw	practically nontoxic
	mallard; acute oral	<292 mg a.i./kg bw	>2250 mg a.i./kg bw	practically nontoxic
	bobwhite quail; 8-d dietary	562 mg a.i./kg diet	>5620 mg a.i./kg diet	practically nontoxic
	mallard; 8-d dietary	<562 mg a.i./kg diet	>5620 mg a.i./kg diet	practically nontoxic
	bobwhite quail; reproduction	300 mg a.i./kg diet	n/a; mortalities were not considered treatment-related	—
	mallard; reproduction	100 mg a.i./kg diet	n/a; treatment-related mortalities occurred at 600 mg a.i./kg diet	—
Mammals	rat; acute oral	n/a	760 mg/kg bw (M; cymoxanil) 418 mg/kg bw (M; Curzate® 60 DF)	moderately toxic highly toxic
	mouse; 90-d dietary	50 mg/kg dw diet (male)	n/a	—
	mouse; 18-month dietary	30 mg/kg dw diet (male and female)	n/a	—
Invertebrates	earthworm; 14-d acute	<125 mg a.i./kg soil	2109 mg a.i./kg soil	—
	honeybees; 48-h contact	25 Fg a.i./bee	>25 Fg a.i./bee	practically nontoxic
	honeybees; 48-h oral	1000 mg a.i./L	>1000 mg a.i./L	practically nontoxic
Terrestrial plants	corn, soybean, cotton, rice, sorghum, spring wheat, crabgrass, barnyard grass, nutsedge, morning glory, cocklebur, wild oats; screening trials	seedling emergence: no effects observed with any plant	n/a	—
		vegatative vigour: #13% phytotoxic effects on corn, rice and crabgrass	n/a	—

Table 5 Summary of effects of cymoxanil on aquatic nontarget species

Organism	Organism and study	NOEC	LC_{50} or EC_{50}	Interpretation
Freshwater invertebrates	*Daphnia magna*; 48-h, static	15 mg/L (immobility)	28 mg/L	slightly toxic
	Daphnia magna; 21-d	0.067 mg/L (adult mortality and first day to reproduction)	0.34 mg/L	—
Marine invertebrates	mysid shrimp; 96-h	6.09 mg/L (mortality)	> 44.4 mg/L	slightly toxic
	mysid shrimp; 28-d	1.70 mg a.i./L (reproduction)	n/a	—
	eastern oyster; 96-h, shell deposition	28.2 mg/L (shell deposition)	> 46.9 mg/L	slightly toxic
Freshwater fish	bluegill sunfish; 96-h, static	17 mg/L (mortality and sublethal)	29 mg/L	slightly toxic
	carp; 96-h, static	47 mg/L (mortality and sublethal)	91 mg/L	slightly toxic
	rainbow trout; 96-h, static	47 mg/L (mortality) 28 mg/L (sublethal, dark colouration)	61 mg/L	slightly toxic
	rainbow trout; 21-d, flow-through	0.22 mg/L (length and wet weight)	1.5 mg/L	—
	rainbow trout; 90-d, fish early life-cycle	<0.031; adverse effects at all test concentrations	n/a	—
Marine fish	sheepshead minnow; 96-h, flow-through	11.3 mg/L (mortality)	>47.5 mg/L	slightly toxic
	sheepshead minnow; 36-d early life-stage, flow-through	0.0942 mg/L (survival at test termination)	n/a	—
Freshwater algae	*Anabaena flos-aquae*; 120-h, static	0.0652 mg/L	0.231 mg/L	—
	Selenastrum capricornutum; 120-h	23% growth inhibition at 1.050 mg/L; one test concentration	>1.050 mg/L	—
	Navicula pelliculosa; 120-h	0.0633 mg/L	0.202 mg/L	—
Marine algae	*Skeletonema costatum*; 120-h	2% growth inhibition at 0.916 mg/L; one test concentration	>0.916 mg/L	—
Vascular plants	duckweed; 14-d, static	2.5–4.2% inhibition at 0.700 mg/L; one test concentration	> 0.70 mg/L	—

Table 6 Summary of risk assessment to terrestrial nontarget species

Organism	Study	NOEC or NOEL	EEC	Margin of safety[2]	Risk	Mitigative measures
Bobwhite quail	acute oral	175 mg/kg bw	113.4 mg/kg diet	2 days	no risk	not required
	8-d dietary	562 mg/kg diet		5		
	reproduction	300 mg/kg diet		3		
Mallard	acute oral	<292 mg/kg bw	32.0 mg/kg diet	10 days	no risk	not required
	8-d dietary	<562 mg a.i./kg diet		18		
	reproduction	100 mg/kg diet		3		
Rat[1]	acute oral (cymoxanil)	LD_{50} = 760 mg/kg bw	476.8 mg/kg diet	18 days	no risk	not required
	acute oral (Curzate® 60 DF)	LD_{50} = 418 mg/kg bw		10 days		
Mouse[1]	90-d dietary	50 mg/kg dw diet (male)	473.9	0.1	no risk[3]	not required[3]
	18-month dietary	30 mg/kg dw diet (male and female)		0.06		
Earthworm	14-d acute	<125 mg/kg soil	0.163 mg/kg soil	>77	no risk	not required
Honeybees	48-h contact	25 Fg a.i./bee	>28 kg/ha	n/a	no risk	not required
	48-h oral	1000 mg a.i./L				
Terrestrial plants	seedling emergence	no effects observed with any plant	135 g a.i./ha for one application and 945 g a.i./ha for seven applications	n/a	no risk	not required
	vegetative vigour	#13% phytotoxic effects on corn, rice and crabgrass		n/a	minimal risk	not required

1 The assessment of the risk of cymoxanil to wild mammals is based on the evaluation of mammalian toxicity studies by the Health Evaluation Division.

2 For acute toxicity studies with birds and mammals, the margin of safety is reported with the unit of days. LD_{50} and NOEC values, as well as food consumption and mean body weights of control animals, were used to determine the amount of time required for a wild animal to accumulate a toxic dose of cymoxanil if exposed to food sources that are contaminated with cymoxanil.

3 It is unlikely that high concentrations of cymoxanil will be sustained on vegetation for an extended period of time (>40 days), owing to the relatively short half-lives that have been reported for cymoxanil. Also, as potatoes are grown over a period of approximately 4–5 months, applications may be spaced further apart than was assumed for this assessment. Environmental concentrations in vegetation could build up over the period that applications are taking place, but should not be present for long periods at the high cumulative levels calculated for seven consecutive applications. As a result, cymoxanil will not pose a risk to wild mammals on a long-term basis.

Table 7 Summary of risk assessment to aquatic nontarget species

Organism	Study	NOEC (mg/L)	EEC (mg/L)	Margin of safety	Risk	Mitigative measures
Daphnia magna	48-h	15	0.089	169	no risk	not required
	21-d	0.067	0.089	0.8	risk	required
Mysid shrimp	96-h	6.09	0.089	68	no risk	not required
	28-d	1.7	0.089	19	no risk	not required
Eastern oyster	96-h shell deposition	28.2	0.089	317	no risk	not required
Bluegill sunfish	96-h	17	0.089	191	no risk	not required
Carp	96-h	47	0.089	528	no risk	not required
Rainbow trout	96-h	28	0.089	315	no risk	not required
	21-d	0.22	0.089	2.5	no risk	not required
	90-d early life-stage	<0.031	0.089	0.3	risk	required
Sheepshead minnow	96-h	11.3	0.089	127	no risk	not required
	36-d early life-stage	0.0942	0.089	1	risk	required
Anabaena flos-aquae	120-h	0.0652	0.089	0.7	risk	required
Selenastrum capricornutum	120-h	1.05	0.089	12	no risk	not required
Navicula pelliculosa	120-h	0.625	0.089	0.7	risk	required
Skeletonema costatum	120-h	0.916	0.089	10	no risk	not required
Lemna gibba, duckweed	14-d	2.5–4.2% inhibition at 0.70	0.089	8	no risk	not required