Re-evaluation Decision

(2,4-Dichlorophenoxy) acetic Acid [2,4-D]

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Re-evaluation Decision for 2,4-D

After a thorough re-evaluation of the herbicide (2,4-dichlorophenoxy)acetic acid [2,4-D], Health Canada’s Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act and Regulations, has decided to allow continued registration for the sale and use in Canada of certain products containing 2,4-D.

- Products containing 2,4-D do not pose unacceptable risks to human health or the environment. They also have value for lawn and turf, agriculture, forestry and industrial uses when used according to the label directions proposed in previous consultation documents. As a condition of the continued registration of these 2,4-D products, new risk-reduction measures must be included on product labels. In addition, registrants must submit additional confirmatory scientific information, identified in this document.

- Some products and uses of 2,4-D are being phased out because the risks exceed current health and environmental standards or there was a lack of adequate data for assessment. This includes all products containing the diethanolamine (DEA) form of 2,4-D and products for aquatic uses.

The regulatory approach for the re-evaluation of 2,4-D was proposed in two consultation documents.¹

- Proposed Acceptability for Continuing Registration PACR2005-01, Re-evaluation of the Lawn and Turf Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D]
- Proposed Acceptability for Continuing Registration PACR2007-06, Re-evaluation of the Agricultural, Forestry, Aquatic and Industrial Site Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D].

A summary of the comments received in response to the consultation on lawn and turf uses, and PMRA’s responses to those comments is presented in Re-evaluation Note REV2006-11, Lawn and Turf Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D]: Interim Measures.

This Re-evaluation Decision document² describes this final stage of the PMRA’s re-evaluation of 2,4-D and summarizes the Agency’s decision and the reasons for it. Appendix I includes a summary of comments received during the consultation process for non-turf uses, and the PMRA’s response to these comments. This decision is consistent with the proposed re-evaluation decisions stated in Proposed Acceptability for Continuing Registration documents PACR2005-01 and PACR2007-06 and Re-evaluation Note REV2006-11. To comply with this decision, registrants of products containing 2,4-D will be informed of the specific requirements affecting their product registrations and of the regulatory options available to them.

¹ “Consultation statement” as required by subsection 28(2) of the Pest Control Products Act.

² “Decision statement” as required by subsection 28(5) of the Pest Control Products Act.
What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the Pest Control Products Act is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration\(^3\). The Act also requires that products have value\(^4\) when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous, modern and consistent with international standards. These methods consider the unique characteristics of sensitive populations in humans (e.g. children) and organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA’s website at [www.pmra-arla.gc.ca](http://www.pmra-arla.gc.ca).

What is 2,4-D?

2,4-D is a selective systemic phenoxy herbicide that mimics the plant growth regulator indole-3-acetic acid (also known as auxin). It is registered for the control of broadleaf weeds, weedy trees and brush, and aquatic weeds after they emerge. Use is permitted on fine turf, aquaculture (oyster farms), aquatic non-food sites, forests and woodlots (conifer release and forest site preparation), terrestrial feed and feed crops, and industrial non-food sites (non-cropland). The different forms of 2,4-D (acid, amine salts and esters) are formulated as emulsifiable concentrate/emulsion, solution, suspension, soluble or wettable granules, granules and pellets. Products containing 2,4-D can be applied by ground equipment or by air.

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\(^3\) “Acceptable risks” as defined by subsection 2(2) of the Pest Control Products Act.

\(^4\) “Value” as defined by subsection 2(1) of the Pest Control Products Act: “the product’s actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product’s (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact”. 
Health Considerations

Can Approved Uses of 2,4-D Affect Human Health?

2,4-D is unlikely to affect your health when used according to the revised label directions. Additional risk-reduction measures are required on 2,4-D labels.

People can be exposed to 2,4-D when consuming food or water, when working as a mixer/loader/applicator or when entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only those uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than the levels to which humans are normally exposed when using 2,4-D products according to label directions.

Additional protective measures including increased personal protective equipment and improved work practices will be included on product labels to further reduce the level of human exposure to 2,4-D. In addition, specific toxicity information regarding symptoms of overexposure are required in the TOXICOLOGICAL INFORMATION section of commercial product labels (see Measures to Minimize Risk later in this document).

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to 2,4-D was estimated from residues in treated crops and drinking water, including the most highly exposed subpopulation (e.g. children 1 to 6 years old). This aggregate exposure (i.e. to 2,4-D from food and drinking water) represents less than 16.3% of the acute reference dose for the most exposed population group (females of childbearing age) and less than 9.9% of the acute reference dose for all other population groups. For chronic risk, the aggregated exposure represents less than 24% of the chronic reference dose for all population subgroups.
The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *Food and Drugs Act* through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for 2,4-D are currently specified for asparagus, citrus fruits, and cranberries or processed foods derived from these foods. Where no specific MRL has been established, a general MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. Proposed changes regarding the definition of the residue of concern for 2,4-D residues in food are detailed in PACR2007-06.

**Risks in Residential and Other Non-Occupational Environments**

**Non-occupational risks are not of concern**

Risks to homeowners and their children from contact with treated lawns and turf are not of concern.

**Occupational Risks From Handling 2,4-D**

**Occupational risks are not of concern provided additional risk-reduction measures are observed.**

The risk estimates associated with applying, mixing and loading activities for label uses are acceptable for all scenarios approved for continued registration, provided the label directions are respected, including the limits on the amount of product handled per day for some formulations/uses and the personal protective equipment indicated. These measures are needed to minimize potential exposure and protect worker health.

**Postapplication risks to workers are not of concern provided additional risk measures are observed.**

Postapplication occupational risk assessments consider exposures to workers entering treated agricultural, forestry, aquatic and industrial sites. Based on the precautions and directions for use on the original product labels reviewed for this re-evaluation, the risks to workers performing certain high-exposure activities after the product is applied are of concern.

Protective measures to reduce worker exposure for certain use scenarios were proposed in the consultation documents and will be implemented for scenarios where appropriate. In addition to protective equipment, these measures include lengthened restricted-entry intervals (REIs) and restricting the amount and concentration of 2,4-D that can be used in some scenarios (see Measures to Minimize Risk later in this document).
Environmental Considerations

What Happens When 2,4-D Is Introduced Into the Environment?

All forms of 2,4-D pose a risk to non-target terrestrial and aquatic plants. 2,4-D esters pose some risk to aquatic invertebrates, fish and amphibians. Additional risk-reduction measures must be observed.

A refined assessment of risks to aquatic life indicates that 2,4-D acid and the amines from runoff and spray drift do not present a risk to aquatic life except to aquatic plants. The esters present some potential minor risks to fish and amphibians from runoff and spray drift. Observing buffer zones to reduce exposure from spray drift can mitigate these risks. The major transformation product 2,4-dichlorophenol (2,4-DCP) does not present a risk to aquatic life. The risk assessment of the concentrations reported in rain showed no risk for aquatic life.

All forms of 2,4-D did not present an acute risk to birds the size of a bobwhite quail or larger (170 grams). However, at the higher application rates used on non-cropland industrial sites and forestry, models predict there can be a slight risk to small birds (robin and sparrow) when they consume 2,4-D in their diet. The models are based on the conservative assumption that 100% of the diet is contaminated; however, given the mobile nature of birds, the exposure would be less. The level of concern for reproductive effects in birds was not exceeded.

For small mammals, all forms of 2,4-D (based on most sensitive endpoints) exceeded both the acute and the reproductive level of concern at the higher application rates used in non-cropland and forestry. The risk of acute dietary effects ranged from low to high, and the risk of reproductive effects to small mammals was moderate to high. The risk assessment for small mammals was also based on the conservative assumption that 100% of the diet is contaminated.

A refined risk assessment of 2,4-D use as a granular soil sterilant (5% w/w 2,4-D acid) indicated that the risk was negligible for birds when consuming granules as a source of grit. For mammals, a refined risk assessment for inadvertent consumption of granules while foraging for food indicated that the risk was also negligible. The level of concern for fish and aquatic invertebrates was not exceeded at the concentrations found in runoff. Continued use of 2,4-D as a soil sterilant does not present a risk of reproductive effects to birds and mammals.

Based on available data, the butoxy ethyl ester form of 2,4-D formulation, registered as an aquatic herbicide, poses a high to very high risk to freshwater and estuarine/marine fish and aquatic invertebrates.

Runoff of the amines or the esters following use of 2,4-D is not likely to present a significant risk to fish and aquatic invertebrates. The risks from spray drift can be mitigated when the buffer zones presented in Appendix II are observed. All forms of
2,4-D present a slight risk to small birds and a higher risk to small mammals at the higher application rates used on non-cropland and forestry. However, this is based on the conservative assumption that 100% of the diet is contaminated.

Based on the environmental risk assessment, the PMRA has concluded that risks to the environment are acceptable with measures to further protect the environment are implemented.

Value Considerations

What Is the Value of 2,4-D?

Today, 2,4-D is the third most widely used herbicide in Canada based on the amount of active ingredient applied. The use of 2,4-D reduces a portion of the economic losses incurred annually by weeds across Canada.

Over the past 40 years, 2,4-D has played an important role in maintaining turf. Without it, the number of broadleaf weed control products presently available to homeowners would be severely limited. Most of the Domestic Class products used to control broadleaf weeds on lawns contain 2,4-D; there are few registered alternatives in Canada.

2,4-D also controls a wide variety of broadleaf weeds in non-turf sites. It has long been recognized as being a superior tank mixing partner with other herbicides. These tank mixes control a broader range of weeds compared to products containing only a single active ingredient, resulting in fewer applications, less soil compaction and reduced costs for growers.

2,4-D is essential for managing groups of weeds resistant to other types of herbicides. After decades of use, there is little evidence of weeds developing resistance to this product.

Although 2,4-D is registered as a Restricted Class product for aquatic uses in Canada, the proposal to phase out this use did not raise any objections from stakeholders. Therefore, the phase-out of aquatic uses is expected to have a negligible impact.

Measures to Minimize Risk

The labels of registered pesticides have specific instructions for use. The directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law.

The risk-reduction measures identified in Re-evaluation Note REV2006-11, Lawn and Turf Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D]: Interim Measures, have been implemented. At this time, risk-reduction measures are being implemented to address potential risks identified in the assessment of non-turf uses. In addition to the measures on existing 2,4-D product labels, these measures are designed to further protect human health and the environment.
Additional Key Risk-Reduction Measures

A. The phase-out of products and uses that do not meet current standards for human health risks and/or risks to the environment

   • Registrants’ sales of all products containing the DEA form of 2,4-D have already been discontinued.

   • Aquatic uses are being phased out.

B. Label upgrades to further increase protection of human health and the environment, as detailed in Appendix II

   • Label statements will more accurately describe the product and its allowed uses.

   • For some uses, the maximum application rates of products and/or the number of applications per year have been revised.

Human Health

   • The TOXICOLOGICAL INFORMATION section of commercial product labels will be updated to provide information about symptoms and treatment for over-exposed individuals.

   • A variety of mitigation measures are required to protect mixers, loaders and applicators with the highest potential for exposure. These include additional protective equipment, maximum amounts of product to be handled in a day, the use of closed cabs or respirators, the use of closed mixer/loader systems, and prohibiting human flaggers when product is applied by air or applying granular products by hand in industrial sites.

   • The number of applications and use rates are being restricted to protect workers entering treated sites. Workers must also observe restricted-entry intervals and wear additional protective equipment.

Environment

   • Product labels are being changed to reduce release of 2,4-D into the environment. Labels will have instructions for minimizing the contamination of water by leaching and runoff, and an ENVIRONMENTAL HAZARDS section that warns of the toxicity of 2,4-D to broadleaf plants in the vicinity of treatment.

   • Labels will also contain statements to protect aquatic and terrestrial habitats that may contain sensitive species. Terrestrial and aquatic buffer zones must be observed. The specific distance depends on the application rate, type of spray equipment and use site.
What Additional Scientific Information Is Being Requested?

The risks and value have been determined to be acceptable when all the risk-reduction measures proposed in the consultation document are followed when using the products accepted for continued registration. To refine the current risk assessment, confirmatory scientific information is being requested from registrants as a result of this re-evaluation, in addition to data requested previously in REV2006-11 (see below). Registrants will be asked to submit this information within specified time frames.

Chemistry

- Recent analytical data are required for all identifiable dioxins and furans\(^5\) from at least five consecutive batches of technical grade product manufactured at each of the registered manufacturing sites of each of the registered technical products.

- An updated Statement Product Specification Form is required for all products to which dimethylamine (DMA) is added during the manufacturing or formulation process. The form must identify the levels of \(N\)-nitrosodimethylamine (NDMA) present in the DMA that is used. This requirement will ensure registrants continue to purchase DMA with extremely low levels of microcontaminants.

Human Health

- A developmental neurotoxicity study in rats using 2,4-D acid, complete with adequate histopathological examination of myelin deposition (Data Code [DACO] 4.5.14). This data requirement is based on evidence of neurotoxicity in guideline and published studies (due 30 September 2009). Additional protective measures have been incorporated into the risk assessment to account for this data gap.

- A multigeneration reproduction study in rats using 2,4-D acid (DACO 4.5.1). Limitations in the existing reproduction study preclude a detailed assessment of potential sensitivity to the young (due 30 September 2009). Additional protective measures have been incorporated into the risk assessment to account for this data gap.

Environmental Risks

- Bioconcentration factors for the 2-ethylhexyl ester (EHE) and the butoxyethyl ester (BEE) in fish (DACO 9.5.6) are required within two years to assess the potential for bioaccumulation.

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\(^5\) Including the 17 substances listed in Table 4 of the Priority Substances List 1

*Polychlorinated dibenzodioxins and polychlorinated dibenzofurans.*
Other Information

The relevant test data on which the decision is based are available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa). For more information, please contact the PMRA’s Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra_infoserv@hc-sc.gc.ca).

Any person may file a notice of objection6 regarding this decision on 2,4-D within 60 days from the date of publication of this Re-evaluation Decision document. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the PMRA’s website (Requesting a Reconsideration of Decision, www.pmra-arla.gc.ca/english/pubreg/reconsideration-e.html), or contact the PMRA’s Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra_infoserv@hc-sc.gc.ca).

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6 As per subsection 35(1) of the Pest Control Products Act.
**List of Abbreviations**

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<thead>
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<th>Abbreviation</th>
<th>Full Form</th>
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<td>2,3,7,8-TCDD</td>
<td>2,3,7,8-tetrachlorodibenzo-(p)-dioxin</td>
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<td>2,4-D</td>
<td>(2,4-dichlorophenoxy)acetic acid</td>
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<tr>
<td>2,4-DCP</td>
<td>2,4-dichlorophenol</td>
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<tr>
<td>2,7-DCDD</td>
<td>2,7-dichlorodibenzo-(p)-dioxin</td>
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<td>ADI</td>
<td>acceptable daily intake</td>
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<td>a.e.</td>
<td>acid equivalent</td>
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<tr>
<td>a.i.</td>
<td>active ingredient</td>
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<td>ASAE</td>
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<td>atmosphere</td>
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<td>CAPCO</td>
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<tr>
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<td>EC(_{50})</td>
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<td>EEC</td>
<td>expected environmental concentration</td>
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<td>EHE</td>
<td>2-ethylhexyl ester</td>
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<tr>
<td>(F_{1a})</td>
<td>first litter of the first filial generation</td>
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<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
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<td>FPT</td>
<td>Federal/Provincial/Territorial Committee on Pest Management and Pesticides</td>
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<tr>
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<td>HD(_5)</td>
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<td>m(^3)</td>
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<td>MOE</td>
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<td>NR</td>
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<td>Pa</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>PACR</td>
<td>Proposed Acceptability for Continuing Registration</td>
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<td>PMRA</td>
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<td>ppm</td>
<td>parts per million</td>
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<td>REI</td>
<td>restricted-entry interval</td>
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<td>toxic equivalency</td>
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<td>TIPA</td>
<td>triisopropanolamine</td>
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<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
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<td>UV</td>
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Appendix I Comments on PACR2007-06 and the PMRA’s Responses

The PMRA received several comments in response to PACR2007-06 from a variety of stakeholders including registrants, non-governmental organizations with interests in human health or the environment, provincial governments, users of 2,4-D in forestry and agriculture, and the general public. Many contained additional data or information for consideration by the PMRA. Some of the comments requested changes of an editorial nature to PACR2007-06, which have been incorporated into the reviews without further discussion and will not be reiterated in this section. The PMRA has consolidated and summarized the remaining comments received and provides responses below.

The comments have been grouped as indicated below.

1.0 Comments with Respect to Chemistry
2.0 Comments with Respect to Human Toxicology
3.0 Comments with Respect to Occupational or Bystander Exposure
4.0 Comments with Respect to the Environmental Assessment
5.0 Comments with Respect to Value

1.0 Comments with Respect to Chemistry

1.1 Comment
The expression of the guarantee causes confusion. Why does the PMRA not adopt the American system, which is clearer.

Response
The guarantee statement is expressed according to current PMRA practice for products in use in Canada.

• The ISO-approved common name is used on the label and not the systematic name as on the label used in the United States.
• The guarantee is expressed in g/L for liquids.
• The label does not make reference to any other ingredients except for the active ingredients.

For 2,4-D, the guarantee statements must be expressed as follows:

Technical products example, solid: 2,4-D ... 95% a.e.
End-use product example, liquid: 2,4-D, present as the dimethlyamine salt ... 500 g/L a.e.

1.2 Comment
The PMRA indicated that levels of toxic equivalent (TEQ) and non-TEQ dioxins are linked, according to data; however, evidence of this has not been found in the literature.
Dioxin content is a function both of reactor temperature and feedstock composition. The whole point of decreasing the feedstock contamination with 2,4,5-trichlorophenol (2,4,5-T) was to alter the ratio that is now said to be constant. How can higher chlorinated dioxins be in 2,4-D without lower chlorinated dioxins being present? It is understood the presence of the higher chlorinated contaminants means that there must have been substantial contamination with the lower chlorinated ones as well because the conditions to manufacture them are similar. The presence of higher chlorinated dioxins occurred most probably because the reactor temperature was quite high and the chlorinated phenol feedstock was impure. Does the PMRA have a chemist on staff with an understanding of the origins of dioxins during manufacturing?

It is now recognised that toxic effects of dioxins are also mediated by mechanisms other than the Ah receptor, throwing into question the TEQ basis for regulation. The toxicities (carcinogenicity, neurotoxicity, immunological and reproductive toxicities, and diabetes) that had been associated with 2,4,5-T continue to be reported by independent researchers, in connection with other phenoxy herbicides, and in association with non-Ah receptor binding dioxins and persistent organic pollutants. Both in vitro and in vivo experiments using 2,7-dichlorodibenzo-para-dioxin (2,7-DCDD) in tests of immune suppression found it to be equipotent to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). Please comment on Kramer et al. (1986) and Holsapple et al. (1986).

It is not known to what extent various dioxins other than the commonly monitored 2,3,7,8-TCDD contribute to toxic effects in the human population. The PMRA should undertake a study of this before coming to any conclusion regarding 2,4-D.

A list of references was provided with this comment.

Response
The PMRA’s numerous chemists, who specialize in pesticide analysis, pesticide characteristics and the fate of pesticides in humans and the environment, are familiar with the conditions of dioxin formation in 2,4-D.

The ratio between dichloro-dioxins (e.g. 2,7-DCDD) and higher chlorinated dioxins is likely to be variable because of many other competing reactions under the conditions where chlorodioxins can be formed. Health effects from lower-congener dioxin contamination would be accounted for in the toxicological test results of 2,4-D.

All major dioxin risk assessments completed to date by the United States Environmental Protection Agency (USEPA), World Health Organization (WHO) and the Joint FAO/WHO Expert Committee on Food Additives state that most, if not all, toxic effects associated with exposure to dioxins are mediated through the Ah receptor. Experimental data with Ah receptor null-allele mice support this (lack of Ah receptor confers resistance to TCDD).
The PMRA reviewed the two references in support of 2,7-DCDD being equipotent to 2,3,7,8-TCDD in tests of immune suppression. Kramer et al. (1986) has no relation to either immune suppression or 2,7-DCDD. The results presented in Holsapple et al. (1986) do indicate that 2,7-DCDD has some immunosuppression activity in female mice. Neither the T-dependent or T-independent antibody response is equipotent to TCDD (more than 100-fold less potent); the in vitro polyclonal antibody response suggests 2,7-DCDD might be 10-fold less potent. To the best of our knowledge, these results have not been repeated in any other laboratory or with other species. One could consider the National Toxicology Program bioassay with 2,7-DCDD as the strongest evidence for its general lack of toxicity, especially when one considers the doses used (0.5 and 1.0% of diet).

2.0 Comments with Respect to Human Toxicology

2.1 Comment
There should be a system of reporting pesticide poisonings and other pesticide-related incidents in Canada.

Response
The PMRA recently established a pesticide incident reporting system. Incidents reported by registrants or the public provide an early alert mechanism for health and environmental risks that require investigation and possible corrective action. The incident reports also provide information for identifying trends after a product is registered that could lead to corrective action, improved practices for the use of pesticides or prevention and education programs in collaboration with users and industry. More information is available at www.pmra-arl.gc.ca/english/legis/aer-e.html.

Since the PMRA’s incident reporting system was launched, the PMRA has received numerous toxicology-related reports on 2,4-D. The reports received were generally minor and included light headedness, nausea, and itching after application of end-use products.

2.2 Comment
Why has the PMRA found 2,4-D acceptable for registration following the re-evaluation when there are studies that show some concern for humans?

A list of studies was provided with this comment. Four of the studies are related to toxicology.

Response
The PMRA examines toxicity data from a number of different mammalian species including mice, rats, rabbits and dogs to assess cross-species similarities and differences as well as species sensitivity. Studies examine short- and long-term effects as well as the potential for a chemical to induce birth defects, to result in reproductive effects and to cause cancer. These studies are conducted at doses many times higher than those to which humans are exposed in order to understand the toxicity profile for a given chemical. Unless there are sufficient data to indicate another species is more appropriate, the most sensitive animal species is used as the indicator species for human toxicity and health risk assessment. The PMRA also assumes that humans are more sensitive to the effects of a chemical than the most sensitive animal species.
The difference between the human exposure level and the no effect level from animal studies is referred to as the margin of exposure or the safety margin. As a minimum, this value must be 100 times below the “no effect level” that has been determined from animal test data, but is often several hundred to greater than 1000 times less. Part of the human health assessment for 2,4-D is to ensure that there is a large enough safety margin between the level to which humans are exposed and any identified toxic effect during animal testing. If the level of human exposure is hundreds or thousands of times less than the no effect level observed in animal testing, the criteria used to define “acceptable risk” has been met. This was the case for 2,4-D.

When the PMRA re-evaluates a chemical, the validity and relevance of published and unpublished studies are determined. If a study is irrelevant or not valid, it is not incorporated into the PMRA’s risk assessment. The PMRA’s assessment of each study referenced in the comment follows.

In the 2005 study by Yilmaz and Yuksel, Swiss Albino mice were administered 2,4-D, dissolved in 70% ethanol, via intraperitoneal injection. The dose was 3.38 mg/kg bw, administered in 3-day intervals. This was a 3-generation reproduction study that looked at enzyme function. Group sizes were 5–10 animals/sex. According to the study authors, 2,4-D and ethanol caused a general increase in malate dehydrogenase when compared to the normal saline group and the ethanol group.

A slight increase in malate dehydrogenase is not considered to be a toxicological risk to any species, including humans. There were also limitations to this study, which include the use of small group sizes, the fact that intraperitoneal injection is an unrealistic exposure scenario for humans and that 2,4-D was dissolved in ethanol. This is problematic because ethanol itself has an effect on liver enzymes. The study authors state the effect of ethanol application was more apparent in the ethanol group than in the 2,4-D + ethanol group. Thus, this study does not add relevant toxicological information to the 2,4-D assessment.

Duchonowicz (2005) presented an in vitro examination of erythrocytes incubated with several compounds, including 2,4-D. The erythrocytes, at 5% hematocrit, were incubated with final concentrations of 1, 2 and 4 mM 2,4-D for 1 hour at 37°C. 2,4-D caused an increase in adenosine triphosphase activity at 1 mM and a decrease in activity at higher concentrations.

In vitro studies are generally conducted to predict a potential effect in in vivo animal studies. In this study, low doses caused an increase in adenosine triphosphase activity and mid- and high-doses caused a decrease in activity, making the toxicological relevance difficult to interpret. Furthermore, numerous in vivo animal studies with 2,4-D did not indicate any effect on erythrocytes. In vivo studies are weighted more than in vitro studies based on relevancy and integrated metabolism of the whole animal. Therefore, these results did not alter the PMRA’s assessment of 2,4-D.
Sturtz and Duffard et al. (2006) measured the amount of 2,4-D in rat milk after maternal exposure to 15, 25, 50 and 70 mg/kg bw/day via diet on postnatal days 1–16. 2,4-D in the milk was evident in a dose-dependent manner. It is to be expected that a number of chemicals can enter the mother’s milk; however, the detection of 2,4-D in breast milk does not necessarily indicate toxicity. This is one of the reasons mammalian reproduction studies are a standard data requirement for pesticides with this use pattern.

Total lipids in the milk were decreased, but not proportionally to the dose. The study states pups had decreased body weight (all doses), but actual data were not presented in the study. The weight loss may be associated with the decrease in milk lipids, but the significance of the weight loss is difficult to interpret because lipid decreases did not adhere to a dose response and the raw data were not provided. It should be noted that in the current guideline reproduction study that was assessed during the re-evaluation of 2,4-D, a no observed adverse effect level (NOAEL) for pup body-weight effects was established at 20 mg/kg bw/day. This NOAEL is 2000× greater than the reference values used to assess acceptability, including the acceptable daily intake (ADI). In other words, any effects noted in this study occur at dose levels far greater (thousands of times) than the level to which humans would be exposed under normal conditions of use.

The PMRA examined many unpublished and published developmental and reproduction studies, including other published studies by the same authors. The PMRA has incorporated the results of these published studies in the 2,4-D risk assessment. In fact, the study by Sturtz and Duffard et al. is considered in the weight of evidence for the requirement of a developmental neurotoxicity study.

De la Rosa (2005) reports a study in which mice were given a single intraperitoneal injection of 50, 100, 150 or 200 mg/kg bw of propanil, 2,4-D or propanil and 2,4-D. There were no reported effects with single herbicide injections; however, doses of 150/150 and 200/200 mg/kg bw of propanil and 2,4-D caused thymic atrophy.

Intraperitoneal injection of chemicals is not a relevant route of pesticide exposure in humans under normal conditions of use. The PMRA also notes that thymic atrophy was only induced at high dose levels and this effect was not apparent in numerous animal studies on 2,4-D. In this study, the NOAEL for thymic atrophy is 100 mg/kg bw, which is almost 6000× greater than both the ADI and the most conservative reference value for occupational exposure used to assess the acceptability of 2,4-D. Therefore, adequate margins of safety for protecting humans from this effect under normal exposure conditions are already inherent in the PMRA’s assessment of 2,4-D.

2.3 Comment
Has the PMRA considered the ban of 2,4-D in Sweden and the associated decline in non-Hodgkins lymphoma (Hardell et al. 2003)?
Response

2,4-D is no longer used in Sweden or Norway, and its use is severely restricted in Denmark. Environmental effects are cited as the primary reason for these actions as 2,4-D has the potential to enter groundwater, the primary source of drinking water in these countries. However, subsequent to these actions, the European Commission, upon completion of its re-evaluation of 2,4-D in October 2001, concluded that 2,4-D was acceptable for continued registration (European Commission 2001).

In the above-cited paper, the authors relate the decline in non-Hodgkin’s lymphoma in Sweden to the ban of phenoxyacetic acids and chlorophenols. However, in the discussion, the authors also state:

Of interest is that the levelling off of the incidence of NHL [non-Hodgkin’s lymphoma] during the 1990s has also occurred in countries other than Sweden. Data from the United States, Finland, and Denmark show a similar trend. However, for Norway and the United Kingdom, no such clear pattern has yet emerged.

Thus, although the United States showed a levelling off of non-Hodgkin’s lymphoma, there was no reported decrease in the use of phenoxyacetic acids. Norway no longer uses 2,4-D, yet there is no decline in non-Hodgkin’s lymphoma. Therefore, the decline of non-Hodgkin’s lymphoma incidence cannot be specifically related to a decrease in 2,4-D use.

A number of other epidemiology studies (both independent and industry-funded) from the United States, New Zealand and Australia report no association between 2,4-D and soft-tissue sarcoma, non-Hodgkin’s lymphoma or Hodgkin’s lymphoma (Smith et al. 1983, Hoar et al. 1986, Woods et al. 1987), and more recent studies have not shown an association between 2,4-D and non-Hodgkin’s lymphoma or other cancers (e.g. Asp et al. 1994, Lynge 1998, Burns et al. 2001). Several major scientific panels have evaluated this body of research and have described the evidence for cancer effect in humans as limited, inconclusive, inconsistent and weak.

2.4 Comment

Various studies report an association between 2,4-D use and breast cancer. Did the PMRA consider these studies in their assessment?

A list of references was included with this comment.
Response
The PMRA examined relevant health-related studies during its evaluation of 2,4-D and reviewed the references provided with this comment. Mills et al. (2005) is an epidemiological case-control study for breast cancer in Hispanic agricultural workers in California. Study results indicate there is no associated increase in breast cancer incidence when all potential chemical exposures were combined. In fact, an increase in chemical uses was actually associated with a decreased incidence of breast cancer. Also, confounding factors such as smoking, previous residence, drinking, diet and family history were not taken into consideration. The study states the following:

...one crop (mushrooms) and three chemicals were associated with breast cancer risks after controlling for known risk factors. Suggestive increases were seen for a phenoxyacetic acid herbicide, 2,4-D, an organophosphate, malathion, and an organochlorine insecticide, chlordane.

The odds ratios for these chemicals are statistically significant. However, with respect to 2,4-D use between 1988–1994, the amount of 2,4-D used was negatively associated with breast cancer. In other words, the more 2,4-D used, the weaker the association.

In 1998, Cornell University published the position paper Cornell University Program on Breast Cancer and Environmental Risk Factors in New York State (March 1998), Pesticides and Breast Cancer Risk, an Evaluation of 2,4-D (Gandhi et al.). This paper states the following.

No differences have been reported in breast cancer rates of women who were previously exposed to 2,4-D through their occupation in either agriculture, manufacture of chlorophenoxy herbicides or service in Vietnam during the war. The few studies that have been done so far are not adequate to assess the risk of breast cancer, since they studied very small groups of women who had been exposed to many other chemicals besides 2,4-D.

This paper also states, “...there is no clear evidence that 2,4-D causes breast tumours in experimental animals.”

2.5 Comment
Can the PMRA comment on Colborn’s paper (2006) in which he concludes the following:

...an entirely new approach to determine the safety of pesticides is needed. It is evident that contemporary acute and chronic toxicity studies are not protective of future generations. The range of doses used in future studies must be more realistic, based on levels found in the environment and human tissue. In this new approach, functional neurologic and behavioural end points should have high priority, as well as the results published in open literature. In every instance, the impacts of transgenerational exposure on all organ systems must be meticulously inventoried through two generations on all contemporary-use pesticides and new pesticides coming on the market. To protect human health, however, a new
regulatory approach is also needed that takes into consideration this vast new knowledge about neurodevelopmental effects of pesticides, not allowing the uncertainty that accompanies scientific research to serve as an impediment to protective actions.

Response
It is widely recognized that all chemicals, including pesticides, have the potential to pose a hazard to human health. Possible adverse health effects include cancer, birth defects, adverse effects on reproduction and development, damage to genetic material and other effects that may impair health. For this reason, an extensive battery of toxicity studies is required to determine the nature and extent of the hazard posed by a pest control product proposed for use in Canada. The required studies are designed to assess the possible adverse health effects on a variety of species that may result from single, multiple or lifetime exposure to a pest control product via the skin, mouth, lungs or eyes. These studies include reproduction and developmental studies designed to assess any potential effects of chemicals on future generations. The studies are conducted using a wide range of doses, including low doses and doses many times higher than those to which humans are exposed to understand the toxicity profile for a given chemical. Also, the use of high doses helps to determine chemical thresholds. The PMRA uses this toxicity profile to determine if additional studies are needed for further characterization. This approach is consistent with other regulatory authorities that base human health risk assessments on animal toxicity data.

Reproductive studies are designed to generate information on possible effects on growth and reproduction, and are conducted over two generations. The dosing period includes pretreatment of males through the period of sperm development and of females through at least one ovulatory cycle. The offspring are exposed to the pesticide through the maternal milk supply until weaning, when they are fed diets containing the pesticide.

Developmental studies are designed to determine whether a chemical may cause adverse effects on the developing fetus. The test substance is administered to pregnant animals during the most sensitive stages of development. These studies provide evidence regarding toxicity to the pregnant animal as well as to the embryo and fetus.

The current database for 2,4-D includes a reproduction study and approximately 15 developmental studies in rats and rabbits. Based on unpublished and published studies, the PMRA has identified a potential neurological sensitivity to the young and, thus, has determined that a developmental neurotoxicity study is required to complete the database. Appropriate uncertainty factors have been incorporated into the risk assessment to account for this data deficiency and to protect the young.

2.6 Comment
How is 2,4-D related to Agent Orange?
Response
Agent Orange was a mixture of 2,4-D and a second herbicide, 2,4,5-T. However, the chemicals used for Agent Orange, and their contaminant levels, were not the same as those commercially available at the time, or since. With the refined manufacturing processes that have been imposed by federal regulatory bodies over the years, contamination of 2,4-D with dioxin levels of concern is not expected. 2,4,5-T was found to be contaminated with TCDD at levels much higher than ever seen in 2,4-D. 2,4,5-T was withdrawn from the market in the early 1980s, in part, because of concerns with dioxins.

2.7 Comment
It has to be emphasized again and again that 2,4-D is an acetylcholinesterase inhibitor and that the symptoms of poisoning are consistent with it and with its ability to poison widespread areas of the brain. Studies by Bernard et al. (1985) and Bukowska and Hutnik (2006) were cited.

Response
There is no indication of widespread neurological effects in the extensive 2,4-D toxicology database. While certain pesticides, such as specific carbamate and organophosphate insecticides, inhibit acetylcholinesterase (AChE), this is not a typical endpoint of concern associated with herbicides such as 2,4-D. The studies that examined the effect of 2,4-D on AChE activity in rat muscle and human red blood cells are not representative of the routes for pesticide exposure in humans. These studies are discussed individually in greater detail hereafter.

Bernard et al. (1985) reported 2,4-D inhibited AChE following intraperitoneal injection of 200 mg/kg bw in rats. Intraperitoneal injection can cause very different effects compared to effects elicited via the typical routes of pesticide exposure (i.e. oral, dermal routes) due to differences in metabolism. However, as noted above, this route is not representative of pesticide exposure in humans. Furthermore, the dose used in this study (200 mg/kg bw) is 12 000 times greater than the ADI or 2500 times greater than the acute reference dose that were established during the re-evaluation of 2,4-D. Thus, the dose used in this in vitro study is far greater than the levels to which humans would be exposed.

In vitro studies are generally conducted to predict potential in vivo effects, which require verification in in vivo studies. In the study conducted by Bukowska (2006), human erythrocytes were incubated with 500 or 1000 ppm of 2,4-D, and a decrease in AChE enzyme activity was noted. The authors considered that protein damage to the AChE enzyme may have resulted either from the direct interaction with 2,4-D or an indirect effect of oxidative stress generated by this herbicide and changes in membrane fluidity.

The 2,4-D toxicology database currently has a one-year rat neurotoxicity study, where animals were dosed with up to 125 mg/kg bw/day of 2,4-D via oral administration. The only effect noted was retinal degeneration at 125 mg/kg bw, resulting in a NOAEL of 75 mg/kg bw/day for this neurological effect. This NOAEL is 4500 times greater than the ADI established during the re-evaluation of 2,4-D. If 2,4-D caused a significant effect on AChE or resulted in delayed neurotoxicity, the neuropathological examination would have identified multiple degenerations.
in the brain after a year of daily exposure. However, no such degeneration was noted in these adult rats. Also, the series of tests conducted to detect neurological damage (i.e. the functional observation battery) would have shown clear effects, but these tests were negative at all doses tested.

Based on the observed retinal damage and a series of published studies that showed decreased myelin degeneration and developmental delays in rat offspring following high prenatal or postnatal doses of 2,4-D (see PACR2007-06), the PMRA is requesting a developmental neurotoxicity study. The required study will examine the relevant neuropathological endpoints, clinical observations and functional observations related to neurological behaviours. As noted in PACR2007-06, the current assessment is protective for these effects by the addition of uncertainty factors to account for the absence of a developmental neurotoxicity study.

### 2.8 Comment

Gandhi recanted the position that 2,4-D is not known to cause cancer in a 2001 Fact Sheet entitled *Pesticides and Breast Cancer Risk: An Evaluation of 2,4-D.* ([http://envirocancer.cornell.edu/FactSheet/Pesticide/FS14.2_4-D.cfm](http://envirocancer.cornell.edu/FactSheet/Pesticide/FS14.2_4-D.cfm)).

**Response**

There is no indication that Gandhi recanted his position on 2,4-D and cancer in the 2001 update of his paper. As in 1998, Gandhi states, “There are no reports that indicate a direct link between 2,4-D exposure and cancer in humans.” While there is concern with respect to non-Hodgkin’s lymphoma, “… results from different studies are not consistent. While one half of the studies indicated higher rates of non-Hodgkin’s lymphoma among populations exposed to 2,4-D, the other half did not.” Gandhi also stated that interpretation of various studies was difficult because 2,4-D exposure was accompanied with exposure to many other chemicals.

### 2.9 Comment

The PMRA has not referenced several recent studies showing an increased incidence of non-Hodgkin’s lymphoma, including Mills et al. (2005) and Chiu et al. (2004, 2006).

**Response**

These studies were considered in the PMRA’s assessment and are cited in the reference list of PACR2007-06.

Mills’s 2005 study is discussed in PACR2007-06 (pg. 11). Although associations between non-Hodgkin’s lymphoma and pesticide use have been reported, according to Chiu et al. (2004), this has not been a consistent finding and warrants further investigation. The 2006 paper by Chiu is not specific to 2,4-D. This study looked at classes of pesticides and determined that the etiology of chromosomal translocations in t(14;18)-positive cases of non-Hodgkin’s lymphoma differs from that of t(14;18)-negative non-Hodgkin’s lymphoma. With respect to the phenoxy herbicides, the farmers **not** using this class of pesticide had a higher incidence of t(14;18)-positive non-Hodgkin’s lymphoma than those farmers using phenoxy herbicides.
These are good examples of cases in which epidemiology studies identify possible associations rather than causation; thus, they must be examined in conjunction with well conducted toxicity studies that are specifically designed to elicit toxic effects over a series of dose levels. Any limitations the study authors’ specified in the published studies must be weighed in conjunction with other data that is available for a particular compound. The etiology of most non-Hodgkin’s lymphoma cases remains unexplained and multiple causal factors are likely. Although weak associations between non-Hodgkin’s lymphoma and pesticide use have been reported, this has not been a consistent finding. The PMRA will continue to assess public information as it becomes available.

2.10 Comment
The PMRA should not use lowest observed adverse effect levels (LOAELs) for the 2,4-D risk assessment.

Response
No LOAELs were used in endpoint selection for the 2,4-D risk assessment.

2.11 Comment
Xie et al. (2005) report 2,4-D exerts both estrogenic and androgenic effects in rainbow trout. These effects may lead to health outcomes as diverse as precocious puberty, obesity and diabetes, and cancers.

Response
The concentrations used in Xie et al.’s study are extremely high and not relevant to concentrations typically found in the environment.

For the human health assessment, the potential for a given pesticide to elicit endocrine modulating (hormonal) effects is currently assessed from animal studies such as multigeneration reproductive toxicity assays and chronic toxicity/carcinogenicity assays. These studies form part of the data requirements for pesticide registration and have the potential to reveal numerous endpoints that may be directly or indirectly related to endocrine disruption. Based on present day standards, no evidence for effects on the endocrine system were noted in the 2,4-D toxicology database. (See also Appendix I, Comment 4.3.3 regarding environmental effects.)

2.12 Comment
Dog studies were discounted because of lower renal excretion. There are increasing numbers of people, including the very young and the aged, with lower and/or compromised renal capacity.

Response
Any variation within a species population, including humans, is accounted for by the application of a standard 10× uncertainty factor for “intraspecies variation.” This approach is consistent with that of other regulatory authorities that base human health risk assessments on animal toxicity data.

2.13 Comment
The PMRA should do power analysis of its decisions, recognizing the limitations of small-sample animal studies.
Response
Power analysis can either be done before or after data is collected. For most human clinical trials, power analysis is done before the trial to determine the projected size of an expected effect in the human population, the sample size needed for the trial, the statistical confidence level for the study and the type of analysis the researchers will use for the data. With regulatory animal studies, the power analysis is done after the study has been completed and uses the obtained sample size and effect size to determine the power of certain effects. Although different types of data warrant different statistical tests, the primary objective is to determine which effects are statistically significant. These statistically significant effects are used to set NOAELs in the studies. Thus, power analysis is an integral component of the PMRA’s assessment.

2.14 Comment
The PMRA should base its decisions on true, experimentally validated NOAELs, using off-the-shelf products, confirmed with experimentation much below the NOAEL.

Response
Animal toxicity data from internationally accepted guideline studies using doses well above those to which humans are typically exposed, combined with exposure data obtained from well designed studies, provides the most useful information for assessing risks to human health. This approach is used by regulatory authorities worldwide. When considering the entire 2,4-D toxicology database, the dose levels tested across the various studies ranged from 1–300 mg/kg bw/day. This dose range provided information on any potential effects both below and above the selected NOAELs.

2.15 Comment
We should not trust industry-sponsored studies.

Response
All pesticide applicants are required to develop a comprehensive database of information that is critically assessed by the PMRA’s scientists to determine if and under what conditions of use a pesticide will pose no harm to environmental and human health. The studies the applicants submit must be conducted in compliance with internationally accepted study protocols. Scientists and regulators design these protocols to produce scientifically valid data. Countries including Canada, the United States, European Union and other members of the Organisation for Economic Cooperation and Development (OECD) have harmonized data requirements and study protocols. These studies are conducted by industry or in industry contracted laboratories and they must be in compliance with good laboratory practice. This ensures in-depth documentation of study conduct and the results produced. Compliance with good laboratory practice gives regulators the ability to audit laboratories, data and study samples to ensure their reliability.
The PMRA scientists can and do reject studies that are deemed to be deficient, that unjustifiably deviate from established study protocols or for scientific issues that affect the ability to interpret the data. The studies industry submits to the PMRA are generally of very high quality. In contrast to published scientific studies, which the PMRA also examines, industry-sponsored studies often include raw data. This translates into thousands of pages of data for a given compound, which undergo thorough analyses and cross-checking between studies to ensure data consistency. As a result of the evaluation of data industry submitted to the PMRA, the PMRA can also request additional data to address concerns arising from the evaluation.

2.16 Comment
Please define higher doses. It is well understood that the term “higher doses” usually means at or near MTD, well above renal saturation. The text should read as follows.

Both 2,4-D-acid and pure DEA induce kidney effects, with brain and spinal cord demyelination occurring at higher doses (above the threshold of saturation of renal clearance), while DEA on its own was positive for immunotoxicity in mice (National Toxicology Program 1992a, 1992b, 1992c, 1994).

Response
With respect to 2,4-D, the demyelination occurred at LOAELs in published studies. While these LOAELs are dose levels above potential renal saturation, the dose levels that could cause potential neurotoxicity in a guideline developmental neurotoxicity is not definitive. It is for this reason that the PMRA refers to “sensitivity” in the PACR2007-06 as “potential.” With respect to pure DEA, there is not enough toxicokinetic information to make this conclusion. The PACR will remain the same and this statement will be reassessed after the submission and evaluation of requested data.

2.17 Comment
The content and intent of the National Toxicology Program’s statement on carcinogenicity requires correction. The text should read as follows:

Additional concerns arise from published data showing that repeated dermal application of DEA on its own has been described as carcinogenic in mice (National Toxicology Program 1999, 2001).

Response
The PMRA assessed the National Toxicology Program data and determined that DEA is carcinogenic in mice. There is no need to revise the wording.
2.18 Comment
Please add wording to define toxic doses in the toxicology profile given the study by Mattsson et al. (1997). The text should read as follows:

Although these effects were observed at much higher dose levels relative to the doses causing the primary target effects (i.e. kidney toxicity at doses above the threshold of saturation of renal clearance) in the short- and long-term studies, these findings may be an indication of offspring sensitivity after exposure to 2,4-D during prenatal and postnatal development.

Based on the results from the current GLP studies, the NOAEL for acute neurotoxicity was 15 mg/kg/day and 75 mg/kg/day for chronic neurotoxicity.


Response
The PMRA agrees to adding the wording (i.e. kidney toxicity at doses above the threshold for renal saturation). The PMRA examined guideline studies and determined that the NOAELs for both acute and short-term toxicity were 75 mg/kg bw/day, with effects occurring at 250 mg/kg bw/day.

2.19 Comment
Please add wording to define high dose for the following passage.

Other effects included a decreased sex ratio (more males) in the F₁₆ generation at the high dose, an increased gestation period, smaller litter size and a marked increase in still births. These high dose effects occurred above the threshold of saturation of renal clearance.

Response
The PMRA will retain the original wording at this time. Renal saturation in the rat likely occurs between 50–80 mg/kg bw/day. Although kidneys from female rats were not examined, maternal toxicity was minimal. An innate compensatory effect for most mammals during pregnancy is the vasodilation and expansion of the kidneys, leading to increased renal output. This is a protective measure so that pregnant females can more readily excrete xenobiotics. Thus, the dams in the study may not have reached a level of renal saturation. However, the PMRA is willing to reassess this wording after the submission and evaluation of requested data.

2.20 Comment
An extra 10× for severity of effect noted for maternal death in rabbit studies is unwarranted. The USEPA does not apply this safety factor in their evaluations.
Response
The PMRA recognizes that the addition of an extra 10× safety factor for maternal mortality in rabbits is not in keeping with the USEPA policy. However, the PMRA is concerned with this effect because of its sudden appearance, consistency across the different forms of 2,4-D and because in some forms of 2,4-D the effect is occurring at 30 mg/kg bw, below renal saturation in rodents, including rabbits. Although the 2,4-D Industry Task Force II (consisting of technical registrants of 2,4-D) claims that renal saturation occurs in rabbits after a 40 mg/kg IV bolus dose, this is not directly comparable to gavage dosing. It is more likely that renal saturation in rabbits, via the oral route of exposure, is greater than 40 mg/kg bw/day.

The extra 10× factor is for seriousness of effect, is in keeping with the PMRA’s current practice, and was endorsed by the 2,4-D Expert Panel.

2.21 Comment
The wealth of information on 2,4-D and its long term use has consistently shown low health risk from the use of 2,4-D. Certain conclusions of the risk assessment presented by the PMRA raise concern that 2,4-D presents potential risks to reproductive, developmental and neurological endpoints in humans. Taken at face value, the PMRA toxicological assessment suggests 2,4-D would be causing frequent injury to human health when, in fact, there are relatively few documented incidents or health effects given its broad use. The key finding is that toxicological hazard only occurs at an exposure level above the threshold of saturation of renal clearance. The PMRA is urged to consider its conclusions regarding toxicity concerns in light of generations of “real world” experience with 2,4-D over the course of over 60 years of use in Canada.

Response
The PMRA recognizes that many effects appear to be occurring near the level of renal saturation. Although the database for 2,4-D is vast, there are uncertainties with respect to certain aspects of reproduction toxicity and developmental neurotoxicity. Additional protective measures have been incorporated into the risk assessment to account for this data gap. Until the required data are submitted and evaluated, the PMRA’s risk assessment must safeguard against these uncertainties. If the submitted data shows a lack of developmental neurotoxicity or reproductive toxicity, this will be reflected in the resulting health assessment.

3.0 Comments with Respect to Occupational or Bystander Exposure

3.1 Comment
Restricted-entry intervals (REIs) for woody plant treatment are unnecessary because these treatments are generally conducted on a spot basis or in localized areas. The public would be much more likely to go around dense woody plant areas rather than enter them.

Response
The PMRA agrees. The bystander REI was removed for woody plant treatment. Bystander risk was still assessed for the broadleaf (i.e. non-woody) plant treatment because these treatments are applied in areas the public could enter and encounter residues following application.
3.2 Comment
The agronomically feasible maximum quantity of technical grade active ingredient to be handled per day (i.e. 8 kg a.e./day for acid, DMA, and EHE products) appears to be reasonable for low pressure application, but not for high-pressure, high-volume handwand application. Agronomically feasible daily use quantities could easily exceed the proposed maximum.

Response
Although data, including an Industrial Vegetation Management Association of Alberta document, were submitted during the comment period, these data did not provide information that could be used for further refinement of the risk assessment.

In the assessment of 2,4-D, margins of exposure (MOEs) for some handwand application scenarios were not reaching the target MOE. To maintain this use, the proposed mitigation measures limited the amount of active ingredient that could be handled per day and increased the personal protective equipment. This limit was considered to be agronomically feasible for low-pressure handwand and backpack application. However, the PMRA acknowledges that the feasibility of the proposed limit decreases as the volume and pressure increase. Although application using high-volume, high-pressure handwands could exceed the proposed limit, the handler has the option of using a lower volume, higher dilution or lower pressure application method to treat the target area. These options allow handlers to apply the treatment without exceeding the daily limit and remain within the exposure level considered to be acceptable.

3.3 Comment
Respirators are unfeasible mitigation for workers using handheld equipment.

Response
As mentioned previously, a limit of the amount of active ingredient that could be handled per day was applied to handheld equipment to allow continuing registration with that type of application equipment even though some MOEs were not reaching the target MOE. To maximize the agronomic feasibility of this limit (i.e. have the limit as high as possible), a respirator was added to the personal protective equipment for non-croplands as an additional means of protection.

Although a respirator may not be feasible for some activities, including it in the mitigation increased the limit of active ingredient handled per day by 65%. This higher limit made certain higher pressure/higher volume application methods more feasible.

As the maximum amount handled per day may not be needed for all types of handheld application equipment, the following label statement will be added to the labels of products containing the acid, DMA and EHE forms to ensure that the additional protection of a respirator would not be required unless a higher amount of product may be used.

For acid, DMA, EHE products used on non-croplands

• Applicators using handheld equipment must wear a respirator if they are going to be handling more than 5 kg a.e. per day (sufficient to treat approximately 112 L/day at the highest rate of 0.0448 kg a.e./L).
• Under no circumstance should applicators handle more than 8 kg a.e. per day (sufficient to treat approximately 179 L/day at the highest rate of 0.0448 kg a.e./L)

Note, however, that a respirator is required using handheld equipment to apply products containing the isopropylamine (IPA), triisopropanolamine (TIPA) or BEE forms because the current limit of kilograms active handled per day is already quite low and lowering it further to remove the requirement for the respirator would be unfeasible.

3.4 Comment
There is concern that the REI of 9 days for non-cropland (annual and perennial) will apply to roadside ditches and rights-of-way. This raises the concern of notification provisions to the public (who will have free access to these areas). Has this been considered?

Response
The REI of 9 days applies to commercial workers only. Risks to the public entering these areas following treatment were taken into account in the exposure assessment and do not warrant an REI.

3.5 Comment
Does the PMRA have any specifications for closed cabs?

Response
A closed cab is a chemical-resistant barrier that completely surrounds the occupant of the cab and prevents contact with the pesticide or treated surfaces outside the cab. There are two types of closed cabs:

• cabs with physical barriers only to prevent direct exposure—enclosed tractor cabs, closed aircraft cockpits, etc.
• cabs that provide respiratory protection— incorporating a dust/mist filtering and/or vapour/gas purification system—in addition to the physical barrier

The latter must be specifically certified by an appropriate authority.

3.6 Comment
REIs for hand detasselling activities are not appropriate for sweet corn.

Response
The PMRA agrees. The REIs for hand detasselling sweet corn were removed from the label requirements. In addition, the following statement is now required.

Do not detassel sweet corn by hand.
3.7 Comment
Could the PMRA provide a clear description of handheld equipment; PACR2007-06 does not define it.

Response

Handwand
A handwand is a lightweight, hand-operated sprayer. Its name is derived from the long metal extension that ends in an adjustable nozzle. A hose attaches the “wand” to a small portable tank or larger, stationary one. This type of sprayer can vary widely in type and pressure. The most commonly seen handwands are compressed-air sprayers. The applicator may need to “shake” portable tanks to assure the chemicals are mixed properly. They are often used for spot herbicide application in fields, crack and crevice treatments, along roadsides and in greenhouses.

Backpack
A spray tank that fits comfortably on the back like a knapsack. It contains a hand-operated pump, a pressure chamber, lance with an on/off tap or trigger valve and one or more nozzles. A UV-light inhibitor is usually incorporated into the plastic. The usual tank capacity is about 15 litres so that the tank weight is not excessive to the handler. The volume of the tank is indicated by graduated marks, moulded in plastic tanks.

3.8 Comment
Could you clarify the sites where there is a specified maximum amount of active ingredient that can be applied in a day?

Response
The maximum amount of product handled per person per day applies to all areas where a particular application may be used, including farmlands, roadsides, rights-of-way, railways, pipelines and highways, airports, industrial parks, wasteland, vacant lots, fence rows. For example, the limit of 2.7 kg a.e applies to workers using handheld equipment when applying to agricultural lands and rights-of-way.

3.9 Comment
It is unclear what the maximum proposed rate is for 2,4-D on rights-of-way.

Response
For 2,4-D acid, DMA and EHE forms, the maximum application rate is 4.48 kg a.e./ha for woody trees and brush control, and 2.24 kg a.e./ha for broadleaf plant control. For 2,4-D IPA, TIPA and BEE, the maximum application rate is 2.24 kg a.e./ha for woody trees and brush control as well as broadleaf plant control.

3.10 Comment
It is not clear how wearing coveralls will reduce exposure by 90% and adding a respirator by another 90%. This seems to be an over-estimation and would not be protective in the context of take-home and vehicle contamination.
Response
The PMRA, USEPA and the California Department of Pesticide Regulation developed these protection factors to estimate the reduction in exposure that wearing increased clothing would provide. For dermal body exposure, a protection factor is applied to the unit exposure value for the body (legs, arms, torso) for someone wearing a long-sleeved shirt and pants. For cotton coveralls, this protection factor is 75%; for chemical-resistant coveralls, it is 90%. For inhalation exposure, a 90% protection factor for a respirator is applied to the inhalation unit exposure value.

These values were based on a regression of data found in the literature for a variety of materials. Some of these data can be found in a California Department of Pesticide Regulation document that summarizes data from a number of field trials conducted by the Worker Health and Safety Branch and data from published study reports (Thongsinthusak et al. 1991).

Although these protection factors do not apply to take-home and vehicle contamination, a number of statements on the label outline good hygiene practices and include the proper procedures for minimizing take-home and vehicle contamination, such as rinsing gloves before removing them and instructions for disposing of clothing heavily contaminated with pesticides.

Biomonitoring studies have measured exposure levels in the children and wives of farmers that used 2,4-D. Some of the participants sampled in these studies had helped to apply the pesticide. In over 80% of the urine samples, 2,4-D was not detected. More than 80% of the sampled children and women had samples that were negative for 2,4-D in their urine. Those participants that did have detectable levels of 2,4-D had very low levels in their urine (mean of approximately 3 µg/L), indicating that exposures were generally lower than what was estimated in the PMRA risk assessment that concluded acceptable risk at higher exposure levels.

As discussed in Re-evaluation Note REV2006-11, Comment 8.1, biomonitoring studies have also measured exposure levels of bystanders who live near application sites after 2,4-D is used. No detectable 2,4-D residues were found in any bystander urine samples collected for four days following exposure.

3.11 Comment
Many children spend time in the heat with bare skin against the ground in pick-your-own berry patches. It is not clear that their increased absorption and susceptibilities are addressed.

Response
Use of 2,4-D on berry plants is limited. Berries are broadleaf plants and, therefore, sensitive to 2,4-D. As such, 2,4-D is normally applied between rows. Use is limited to before planting and after harvest in these crops, and cannot be used within 30 days of harvest. Subsequently, the concentration of 2,4-D in soil would be low during harvest activities. The application rate for berries is lower than the application rate for turf—0.46–1.25 kg/a.e ha for berries versus 1.25–1.75 kg a.e./ha for turf. Therefore, the turf risk assessment for children would encompass exposure when children are picking berries.
As presented in PACR2005-01, the turf risk assessment evaluated exposure in children playing on treated turf immediately after application. This was considered to be a high-end exposure scenario because it was assumed children would be exposed dermally through contact with treated turf as well as orally through ingestion of soil, turf mounting and hand-to-mouth contact. The unique physiology, behaviours and play habits, such as their lower body weights and hand-to-mouth contact while playing, were also taken into consideration in the exposure assessment.

In addition, extra safety factors were applied to the no effect level identified in animal toxicity studies to protect population groups, such as children and pregnant women, that may be more susceptible to the potential effects of pesticides. This resulted in reference doses that were 300- to 1000-fold lower for these sensitive groups, which are more protective than the minimum 100-fold safety factor. Thus, products will not be considered acceptable for continued registration unless the estimated human exposure is at least 300 times to 1000 times less than the level at which there were no observed effects in the studies examined. These levels ensure the most sensitive population groups—children and pregnant women—are protected.

4.0 Comments with Respect to the Environmental Assessment

4.1 Comments Related to Factors that Affect the Size of Buffer Zones

4.1.1 Comment
A number of assumptions that are used in the buffer zone modelling process include application rate, release boom height, windspeed, nozzle classification, droplet size, water volume and toxicity endpoint. There may be opportunities for the PMRA to reconsider the assumptions made for some of these that do have more significant impact.

The current spray operations are with winds less than 10 km/hour. If all of the buffer zone data are based on 16 km/hour, the required buffer zones do not reflect what is taking place. The AgDisp modelling using coarse droplet size is reasonable, but the details of modelling could be key issues. Need details of other critical parameters including release height, relative humidity and canopy interception.

Response
1) Boom Height
Regarding release boom height, the PMRA uses an aerial release height of 15 m, which is a generous value given that in practice most pilots fly at higher levels (20 or 25 m) for safety. Lowering the release boom height to 5 m is not feasible because pilots are hesitant to fly this low due to safety concerns.
2) **Spray Droplet Size**
Regarding spray quality, the PMRA computed the aerial buffer zones for coarse droplet size at the request of the 2,4-D Task Force II as a means of reducing the buffer zones. The 2,4-D Task Force II indicated to the PMRA that coarse droplet size would be efficacious; however, very coarse or extremely coarse droplet size may not necessarily be efficacious. To recompute the buffer zones for larger droplet sizes, the PMRA would need confirmation from industry and users regarding the efficacy of 2,4-D with larger droplet sizes.

3) **Wind Speed**
a) The PMRA computed the buffer zones for a maximum wind speed of 16 km/hour. This allows users to spray products containing 2,4-D at wind speeds up to this maximum limit. If growers and applicators wish to lower the maximum wind speed to another value, the PMRA is willing to accommodate this request. However, they must indicate to the PMRA that an agreement has been reached on a particular value that the PMRA will then use to recompute the buffer zones. This new lower wind speed would then be added to the label as the new maximum wind speed at which the product can be applied.

b) The suggested rewording of the label is not necessary as the proposed label statements in PACR2007-06 indicate the upper limit for wind speed (16 km/hour) and that buffer zones are only required for downwind areas where there will be spray drift, not upwind areas. In addition, the buffer zone tables indicate that they are for coarse droplet size only. Medium or other droplet sizes are not an option for the user. The buffer zone model is calculated assuming that the aircraft is flying at minimum height above the canopy (15 m), which is lower than that used in practice in most circumstances.

4) **Canopy interception**
The PMRA uses a 50% canopy interception factor when calculating buffer zones for forestry.

5) **Type of aircraft and application technology**
a) The difference in buffer zones between a fixed wing and a rotary wing aircraft is the result of various factors such as fewer nozzles on a rotary wing aircraft, differences in swath width, differences in airspeed and other factors that affect spray drift.

b) In response to comments that different application technologies are not included on the label statements, the PMRA computes buffer zones for the application technologies for which information has been submitted. If it is desired that other application technologies be included on the label, the PMRA is willing to accommodate this and invites the submission of specific information that can be used to evaluate the technologies.
c) With regard to comments about various factors that help to apply the product (e.g. electronic guidance, remote sensing, etc.) and add precision and accuracy to spray operations, these technologies will not reduce spray drift or buffer zones. Buffer zones are calculated assuming the flight path is flown accurately. Therefore, a greater precision will not reduce the buffer zones.

6) Calculation of buffer zones
a) The buffer zone calculations are risk based (the greater the risk, the larger the buffer zone). Buffer zone calculations are carried out using rates of application and toxicity data provided by the 2,4-D Task Force II. Aerial buffer zones are calculated using the AgDisp v. 8.15 model, which has been validated. The inputs for the model for 2,4-D are supplied under the response for Comment 4.3.

b) Regarding concerns that calculations for aerial applications have been done for nighttime conditions, the atmospheric stability module is a new, untested feature of the AgDisp model. The only parameter that has been verified is the “Night Overcast” option.

7) Toxicity data
a) Regarding comments on whether buffer zones are based on the toxicity data for birds and mammals, the terrestrial buffer zones are not based on the toxicity of 2,4-D to birds and mammals, but rather on the toxicity data for plants.

b) The PMRA has encouraged pesticide registrants and the 2,4-D Task Force II to provide toxicity data from more relevant plants that occupy an edge-type habitat to reduce buffer zones rather than data from sensitive crops.

c) Buffer zones are intended to protect sensitive terrestrial habitat downwind of the spray application site and are not intended to protect specific crops from spray drift. The buffer zones for 2,4-D were based on toxicity data on the tomato supplied by the 2,4-D Task Force II. This plant was chosen as it was the most sensitive of all plants tested. To refine the risk assessment, submitted toxicity data on 12 crop species have now been used to obtain an endpoint based on species sensitivity distribution that is reflective of a wider range of species.

d) Regarding concerns raised about the toxicity endpoints used in the risk assessment for aquatic life, the PMRA has revised its risk assessment methodology for aquatic life since the publication of PACR2007-06, resulting in changes to the toxicity endpoints used. A refined risk assessment for aquatic life has been completed and the corresponding buffer zones have been adjusted accordingly. Separate buffer zone tables have been produced for the acid/amine derivatives and the ester derivatives. Using the refined approach, the chronic no observed effect concentrations (NOECs) are not used in the revised buffer zone calculations for 2,4-D. The data on the EHE half-life in water were taken into consideration along with other data in the risk assessment for aquatic life. With
respect to using other species such as aquatic plants and rainbow trout, the risk assessment is conducted separately on fish, amphibians, aquatic invertebrates and aquatic plants. The aquatic buffer zone calculations include the most sensitive species among the groups above.

e) With respect to comments that there is no evidence of appreciable non-target effects, the PMRA’s position is that, in the absence of such studies, it cannot be assumed there is no non-target impact based on the data available for this risk assessment. Scientific data to support the claim that there is no evidence of appreciable non-target impact should be submitted. In addition, as previously stated, the spray buffer zones are risk based and depend on the application rates and toxicity data on plants submitted by the 2,4-D Task Force II.

4.1.2 Comment
The complexity of the buffer zone table categorized by application technique and crop is inappropriate. Categorization by application technique and application rate would be more appropriate.

Response
Buffer zone calculations for specific crops include cumulative application rates for multiple applications of 2,4-D. Therefore, we cannot provide a buffer zone table simply listing application rates. The buffer zones provided in the table on the label are clearly specified for each use and do not require any further calculation by the applicator.

4.1.3 Comment
Buffer zones for coarse droplet aerial spray are much larger than the provincial buffer zones some applicators currently use (60–120 m).

Response
The buffer zones the PMRA calculated are risk based, and the aerial buffer zones were calculated using the AgDisp v. 8.15 model that used application rates and toxicity data from the 2,4-D Task Force II. Input parameters for the model were reconsidered and those chosen are provided below. The revised buffer zones are all considerably less than 60 m for water bodies >1 m deep. For water bodies <1 m deep, freshwater habitat buffer zones for the acid/amine derivatives are less than the provincial maximum (120 m) with one exception. Buffer zones are larger than the provincial maximum only for the ester derivatives in water bodies <1 m deep. These buffer zones protect amphibians which are sensitive to the 2,4-D ester.
## Input Parameters for AgDisp v. 8.15

<table>
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<tr>
<th>Parameter</th>
<th>Agriculture, Pastures, Rangelands</th>
<th>Forestry, Woodlands</th>
<th>Rights-of-Way, Industrial Sites</th>
<th>Woodlots</th>
<th>Corrals, Feedlots, Holding Pens</th>
<th>Non-Cropland</th>
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<td>Release height (m)</td>
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<td>Flightlines</td>
<td>20—large acreage crops (e.g. cereals, corn, etc.)</td>
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<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
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<td>10—small acreage crops (e.g. alfalfa, clover, vegetables, blueberry)</td>
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<td>0.15 or 0.80 and 2.0</td>
<td>0.15 or 0.80 and 2.0</td>
<td>0.15 or 0.80 and 2.0</td>
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<td>Medium - Systemic insecticides and fungicides, contact and systemic herbicides</td>
<td>Coarse - Generally product-specific, as requested by registrant</td>
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<td>Night overcast</td>
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<td>Air Tractor 401</td>
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</tr>
</tbody>
</table>
### Calculations for Spray Material

**Cumulative Active Rate**

Total amount of active ingredient applied annually, after accounting for transformation/losses (i.e. aquatic or terrestrial time for 50% decline [DT₅₀₈]).

**Cumulative Product Rate**

Equal to (cumulative active ingredient rate ÷ guarantee) × solid granular end-use product

**Active Fraction**

Equal to cumulative active rate ÷ spray volume of × L/ha.

**Non-volatile Fraction**

Equal to [cumulative product rate × (1 - water content)] ÷ spray volume of × L/ha

### 4.2 Other Comments Related to Buffer Zones

#### 4.2.1 Comment
Terrestrial and aquatic habitats should be defined. This would help farmers or applicators. In addition, it would aid technical and enforcement staff to interpret, explain and enforce regulations.

**Response**

Definitions of terrestrial and aquatic habitats can be found in Regulatory Proposal PRO2005-06, Agricultural Buffer Zone Strategy Proposal. The PMRA is in the process of drafting a best management practices booklet that should assist applicators and farmers in identifying terrestrial habitat.

#### 4.2.2 Comment

Buffer zones for terrestrial habitats are not required for spraying rights-of-way. How this pertains to forest uses?
Response
The PMRA has exempted rights-of-way uses from requiring buffer zones to protect terrestrial habitat because complete plant/weed control is required right up to edge of the application areas on these sites to ensure user safety. Rights-of-way through forests are included in this exemption.

4.2.3 Comment
Some of the terrestrial habitats in PACR2007-06 are also registered use sites. Rather than a list of land use types (i.e. grasslands, woodlots, shrublands, etc.), a more general guidance to users on avoiding drift to non-target areas is advised.

Response
Pesticide user groups have asked the PMRA to be more specific regarding land use types on the label. As a result, PMRA is continuing to be specific in our label upgrades.

4.2.4 Comment
Temporary water in prairie landscape makes applying buffer zones non-workable. There is no consensus among various agencies with interests in water habitats and riparian areas on the definitions of what constitutes these areas.

Response
Temporary bodies of water do not require buffer zones. Sloughs, ponds and potholes are not temporary water bodies. The definition of temporary water bodies can be found in Regulatory Proposal PRO2005-06, Agricultural Buffer Zone Strategy Proposal. A temporary water body is:

- an area covered by water only some of the time and the water holding period is not regular or seasonal. An example of this kind of water body is the lower part of a field flooded after a heavy rain or runoff.

Seasonal water bodies do need to be buffered if there is water in them during application. Seasonal water bodies are defined as:

- an area covered with water only part of the year and for which flooding occurs in subsequent years on a regular basis. This will depend on climatic conditions and patterns. An example of this kind of water body is an aquatic area with water in the spring and summer, but dries out in the fall and winter.

4.2.5 Comment
Placing large buffer zones around every potential pothole in western Canada is inappropriate because an unambiguous definition of pothole is lacking.
Response
As described in www.epa.gov/owow/wetlands/types/pothole.html, prairie potholes are depressional wetlands (primarily freshwater marshes) found in the Canadian and American prairies. The prairie potholes fill with snowmelt and rain in the spring and some marshes are temporary, while others may be essentially permanent. Submerged and floating aquatic plants take over the deeper water in the middle of the pothole while bulrushes and cattails grow closer to shore. Wet, sedgy marshes lie next to the upland. The prairie pothole region is an important home to North American migratory waterfowl with many species dependent on the potholes for breeding and feeding.

4.2.6 Comment
The Federal/Provincial/Territorial Committee on Pesticide Management and Pesticides has excluded the user community from their discussions. Creating buffer zones without broadly based consultation does not seem appropriate.

Response
The Federal/Provincial/Territorial Committee on Pesticides Management and Pesticides was established to strengthen federal/provincial/territorial relationships in the area of pest management and pesticides. The Committee also provides advice and direction to federal/provincial/territorial governments on programs, policies and issues. However, the Committee is not an appropriate means for consulting a broad public given their mandate.

The PMRA publishes consultation documents—such as Proposed Acceptability for Continuing Registration document PACR2007-06, Re-evaluation of the Agricultural, Forestry, Aquatic and Industrial Site Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D]—to ensure all Canadians can comment on the acceptability of a proposed decision. Such consultation documents are a requirement under the Pest Control Products Act of 2006.

4.2.7 Comment
The Federal/Provincial/Territorial Committee on Pest Management and Pesticides’ (FPT’s) Pesticides Buffer Zone Working Group does not have representation from forestry. Why?

Response
The mandate of the FPT’s Pesticides Buffer Zone Working Group was to assist the development of agricultural buffer zones, not forestry buffer zone issues.

4.2.8 Comment
Concern was expressed that implementing buffer zones for 2,4-D products is premature considering that the PMRA has not finalized their buffer zone strategy proposal and captured inputs from stakeholders. Buffer zones should be implemented after completion of the strategy and publication of a Best Management Practices booklet.

Response
Regulatory Proposal PRO2005-06, Agricultural Buffer Zone Strategy Proposal does not pertain to the calculation of buffer zones, but provides options to users on how to reduce buffer zones for agricultural applications.
At the time of registration or re-evaluation, all products have buffer zones calculated according to the current standards. The aerial buffer zones for 2,4-D were calculated according to current practice and have been updated to reflect recent improvements in the refinement of the risk assessment. The AgDisp v. 8.15 model was used based on application rates and toxicity data provided by the 2,4-D Task Force II. The buffer zones are only applicable to non-target areas that are downwind of spray drift. Areas which are upwind from spray applications do not require buffer zones.

Reductions of these labelled buffer zones do not come into effect until the buffer zone modification strategy is finalized and the Best Management Practices booklet is published. The PMRA has agreed to provide the necessary training tools for applicators to understand how to implement the buffer-zone reduction options in the Best Management Practices booklet.

The PMRA will also be examining additional methods that could be used for drift control, which could further reduce buffer zones. If major changes were to occur the PMRA could consider revisiting buffer zones in some cases.

4.2.9 Comment
The proposed buffer zones and label statements for 2,4-D should be withheld from labelling until a finalized buffer zone policy has been approved with further stakeholder consultation.

Response
The PMRA uses a risk-based method for calculating buffer zones and has been applying this process to all new product registrations and registered-product re-evaluations since 1995.

4.2.10 Comment
The PMRA is urged to consult experts on the aerial application of pesticides in forestry, such as the Canadian Forest Service and the Ontario Ministry of Natural Resources in developing appropriate buffer zones for forestry use.

Response
The PMRA is part of the SERG-International group and regularly attends its meetings. The PMRA has discussed with members of SERG-International the possibility of a dialogue to resolve forestry challenges. In the case of 2,4-D, buffer zones for forestry uses are no longer required for protecting terrestrial habitat, although they are still required for aquatic habitat.

4.2.11 Comment
Could the PMRA consider reducing buffer zones under lower wind speed conditions and reduced boom height?

Response
Regarding wind speed, the PMRA computes the buffer zones based on a maximum wind speed of 16 km/h. Applicators have the option of spraying products containing 2,4-D at wind speeds up to this maximum limit. With respect to release boom height, the PMRA uses an aerial release height of 15 m, which is a generous value given that, in practice, most pilots fly at higher levels (20 or 25 m) for safety.
4.2.12 Comment
It is not clear why buffer zones would be required to protect terrestrial habitats. All terrestrial areas are habitat for something.

Response
Buffer zones are required to protect these areas as the risk assessment indicates that non-target organisms (including plants) found in these areas are at risk of toxic effects from spray drift.

4.2.13 Comment
The PMRA needs to consider the weed species that are harboured in terrestrial buffer zones. The weeds could also spread to the crop.

Response
The PMRA is aware of this concern and would be interested in any analyses/information that could clarify the contribution of plants in edge habitats to in-field weed infestation rates. Weeds outside of the application site are considered to be natural vegetation and, therefore, potential habitat for sensitive species. However, the buffer zones are intended only for those areas downwind of the application site. Areas upwind of the application site do not require buffer zones.

4.2.14 Comment
The size of the buffer zone requires some flexibility with respect to controlling invasive weeds, preventing weed encroachment, and containing and eradicating weeds as needed. If buffer zones are insisted upon in these situations, unacceptable economic loss will occur. In the long term, additional treatments with multiple spray swaths will be required to control pests that could have been controlled at field edge. Failure to recognize this need will eventually require that more pest control product applications be made to larger areas. This approach is not sustainable, nor does it respect basic integrated pest management principles. Excessively large buffer zones for aerial application and some ground applications will significantly reduce the ability of growers to effectively manage invasive weed species.

Response
The PMRA did approach the provinces to collaborate on implementing buffer zones with provincial noxious weed regulations; however, the issue is currently unresolved. The issue of invasive weeds will be addressed at a future workshop being planned by the PMRA in 2008 on defining terrestrial habitats.

4.2.15 Comment
It is unclear whether windbreaks are considered part of sensitive terrestrial habitats. Windbreaks are often within a 4 metre distance from the edge of a crop. Many Ontario growers have planted windbreaks to be good environmental stewards. One reason windbreaks are used is to catch drifting pesticides. If windbreaks were included in the definition for terrestrial habitats, this would contradict the use of windbreaks and could discourage new plantings of windbreaks.
Response
At present, windbreaks are considered part of sensitive terrestrial habitat. The PMRA is currently examining the issue of terrestrial habitats and what types should be included and/or excluded. The PMRA is planning a workshop in 2008 to examine this issue. However, based on the data submitted to support the re-evaluation of 2,4-D, windbreaks would be affected by the drifting of 2,4-D.

4.2.16 Comment
Buffer zones should not be required when applying a product adjacent to an area that is an approved use site or contains a predominately species or plant family that is not affected by the active ingredient. For example, a buffer zone should not be required when applying 2,4-D to a field of wheat adjacent to a grassland or meadow where the predominating species is grass. Similarly, applying 2,4-D on wheat, rangeland or a pasture adjacent to a woodland or forest site should not require a buffer zone. Labelled uses of 2,4-D should not be included as sensitive habitats.

Response
Agricultural land does not need terrestrial buffer zones when applying pesticides. 2,4-D is registered for use on rangeland, established pastures and hay lands; hence, buffer zones are not required to protect these three types of sites.

However, in the case of a wheat field adjacent to a grassland or meadow, even though the surrounding may appear to be predominately grass, other species are likely to be present. For example, in mixed grass prairie there are other native plants which are not of the grass species and include endangered species. These may go unnoticed to the untrained eye; therefore, buffer zones are required for grasslands and meadows. Note that this issue will be further discussed in a workshop planned for 2008.

4.2.17 Comment
It is unreasonable to extend buffer zones from 450 to 675 m about shallow <1m depth water bodies from current requirements of 60 to 120 m. This would eliminate the use of 2,4-D products in forestry because wetlands and small streams fit this criterion and are found throughout forest ecosystems. Given there are few if any scientifically documented cases of direct impacts of spray drift associated with long-term use of 2,4-D in forestry, buffer zones are not justified.

Response
Buffer zones are no longer required to protect terrestrial habitat for conifer release or site preparation. They are still required for aquatic habitat during forestry applications. The aquatic buffer zones have been revised according to recent changes in the method for determining toxicity endpoints for aquatic life.

4.3 Comments Requesting Clarification of the Environmental Risk Assessment
4.3.1 Comment
It would be preferable if the expected environmental concentration (EEC) values averaged over a year and are referred to as the annual average EEC values instead of maximum EECs.
Response
The text indicates “The 90th percentile of the peak annual concentrations (maximum EECs) over
the simulation time period was used in the acute risk assessment of freshwater and
estuarine/marine fish and aquatic invertebrates. The 90th percentile of the average of the yearly
concentrations (minimum EECs) over the simulation time period was used to assess the risk of
chronic effects (embryo larval stage) in freshwater and estuarine/marine fish.” The former are
higher concentrations used to assess acute effects. The PMRA calculated the upper 90th
percentile of the yearly peak concentrations for the time window of the simulation from
1943–1999 (56 years). The latter refers to the average concentrations for each year, which are
much lower and are used to assess chronic effects that were calculated at the 90th percentile of
the yearly average concentration over the time window.

4.3.2 Comment
Clarification is required regarding whether the values reported are based on dosing with the
un-neutralized acid. If this is the case, the assessment is incorrect because the un-neutralized
form of 2,4-D has specific toxic effects related to its acidity, yet the un-neutralized form is never
present in the environment.

Response
These data were obtained from the WHO 1997 review of 2,4-D. The WHO report indicated that
the active ingredient in the test was the technical grade acid. The test was reported in Hudson,
Tucker and Haegle (1984). The test data reported for the technical grade acid show that it was
less toxic to the Japanese quail, rock dove, pheasant and mallard duck. Therefore, the Chukar is
considered the most sensitive species and was used in the risk assessment. The data reported in
these sources do not indicate whether the acid was or was not neutralized. However, as 2,4-D is
only a weak acid, we do not believe there would be any significant effects due to the acidity
itself.

4.3.3 Comment
New test protocols that more specifically distinguish between endocrine effects and other types
of toxicity are currently being developed. 2,4-D and other products may be tested using these
new methods when they become available. Regardless of the specific nature of the effects, the
risk quotient values that indicate the level of risk for birds and mammals have been clearly
defined. As such, it is suggested that comments regarding the inability to determine reproductive
effects be removed.

Response
The PMRA believes the statements provided in PACR2007-06 are clear and indicate that 2,4-D
will be evaluated for endocrine effects when test protocols are completed and data becomes
available. With the current information, it is not possible to determine if reproductive effects on
birds and mammals tested are a possible indication of endocrine effects.

4.3.4 Comment
Could the PMRA comment on the estrogenic effects of 2,4-D on fish, as indicated in Xie et al.
(2005).
Response
This paper indicates a potential for 2,4-D to interact with the reproductive endocrine system in freshwater fish. However, it does not provide information on effects endpoints that are typically used in environmental risk assessments (i.e. whole organism effects). Available monitoring data indicate the detection frequency of 2,4-D is less than 0.4% of all samples collected in the prairie provinces, where 2,4-D is widely used. The majority of detections of 2,4-D are at low levels and are generally not sustained for long periods of time. The average concentration of observed detections is about 0.0014 mg/L, which is below the lowest NOEC given in the study cited above. In the review of 2,4-D, the potential for endocrine activity was not ruled out. The PMRA will continue to assess the potential for endocrine activity in fish as more data become available. Test protocols for screening and assessing the potential for endocrine activity are currently being developed and validated. When the appropriate testing protocols have been developed, 2,4-D may be subject to additional screening and/or testing to better characterize any potential effects related to endocrine disruption.

4.3.5 Comment
Based on previously discussed differences between 2,4-D acid, esters and amines, it is suggested that they not be grouped together for the environmental review.

Response
The toxic effect of the amines and the acid are considered to be similar but distinct from the ester forms as indicated by the 2,4-D Task Force II. The toxicity values are reported separately for the acid and amines (as one group) and the esters as another group. The amines rapidly dissociate in the presence of water into a 2,4-D acid anion and a corresponding cation.

4.3.6 Comment
Given the lack of observed toxicity under field conditions, the level of risk to small birds and mammals appears to have been overestimated. 2,4-D is applied only once in a crop and is degraded too rapidly in the environment to present an exposure that approaches 10% of the diet over a typical lifetime of any species of small mammal. The foods birds typically consume are unlikely to contain significant residues of 2,4-D.

Response
The screening level risk assessment for 2,4-D is based on conservative assumptions, i.e. the maximum dose using the longest half-life of 2,4-D. Thus, the risk quotient values presented are considered to be “reasonable worst case scenario values.” Given there are no toxicity data available for the robin and the sparrow, data were obtained by extrapolation (based on body weight) from the toxicity data for the Chukar (designated as the most sensitive species) using a method provided by the Canadian Wildlife Service. The PMRA recognizes that there is a level of uncertainty in the risk assessment as there was insufficient data available to carry out a refined risk assessment. However, it is expected the exposure will be less than that estimated in most instances because birds will also feed from other sources not treated with 2,4-D. As the half-life of 2,4-D is generally quite short and based on the reproductive risk assessment for the Bobwhite, it is not likely to be a risk to small birds.
4.3.7 Comment
Henry’s law constant should be changed from $7.26 \times 10^{-6}$ Pa m$^3$ mol$^{-1}$ to $4.74 \times 10^{-10}$ atm m$^3$/mol at 25°C.

Response
These are different expressions of the same number. Henry’s law constant $K = \text{Vapour Pressure} \times \text{Molecular Mass} / \text{Molar Solubility}$ is calculated as $7.26 \times 10^{-6}$ Pa m$^3$/mole at 25°C or $7.17 \times 10^{-11}$ atm m$^3$/mole using a molar mass for 2,4-D acid of 221 g/mole, vapour pressure of $1.87 \times 10^5$ Pa and a water solubility of 569 mg a.i./L. The dimensionless reciprocal partition coefficient $1/H$ is calculated as $3.41 \times 10^{-8}$.

4.3.8 Comment
Clarification is required regarding the transformation of the esters.

Response
The sentence will be reworded in the review as follows:

The esters transform to the acid via hydrolysis and biotransformation over the course of a few hours at applications rates of 4.48 kg a.e./ha and lower. At the high application rates used in aquatic weed control (19.0–42.75 kg a.e./ha), available field data indicate that a small fraction of the ester form may be present for longer periods of time.

4.3.9 Comment
“The half-life from studies on crops (wheat and corn) is 16 days for the acid and amines and 5 days for the ester (ester + 2,4-D acid residue)” should be revised to “the half-life from studies on crops (wheat and corn) is 7 days for the acid and amines and 8 days for the esters (ester + 2,4-D acid residue).”

Response
Risk quotients are calculated for the minimum (0.329 kg a.e./ha) and maximum (4.48 kg a.e./ha) application rates. For multiple applications (2 at 2.24 kg a.e./ha), the cumulative application rate (see PACR2007-06, Section 5.1) for the risk assessment of seedling emergence is calculated using the upper 90th percentile of the distribution of half-lives on bare soil for the acid and amine group (10 day) and the upper 90th percentile of the distribution of half-lives for the ester group (8 day). For the risk assessment of vegetative vigour, the cumulative application rate is calculated using the longest half-life on foliage for the acid and amine group (16 day) and the longest half-life for the ester group (5 day). The calculation was based on the available field data.

4.3.10 Comment
The PMRA indicated the measurable half-lives of 2,4-D in anaerobic biotransformation studies vary from 41 to 1610 days. Would it not be more accurate to say the measurable half-life of 2,4-D acid in this study was 41 days. This value is also representative of 2,4-D DMA because of its almost immediate dissociation to 2,4-D acid in a natural environment.
Response
The suggested wording is misleading and indicates that the anaerobic half-life of 2,4-D is only 41 days. The study results indicate a very wide range in anaerobic half-lives. The half-life in the study with 2,4-D acid was 41 days, and with DMA, 1610 days. In the latter case, the applied active ingredient was DMA. The latter study is really indicative of the anaerobic half-life of 2,4-D acid because DMA dissociates very rapidly in the presence of water to a 2,4-D acid anion and a corresponding cation. Therefore, the studies indicate a very wide range in half-lives for the 2,4-D acid. To clarify this point, the wording will be changed to read as “Measurable half-lives of 2,4-D acid and the amines in anaerobic biotransformation studies vary from 41 days to 1610 days”. This removes the confusion from the association of the half-life values with a particular derivative.

4.3.11 Comment
The earthworm LC50 for DMA is inconsistent between PACR2005-01 and PACR2007-06. Please clarify.

Response
The 291 mg a.e./kg soil (DMA) in PACR2005-01 should have read as 350 mg DMA/kg soil. The measured substance was DMA, not acid equivalent (a.e.). If the value 350 mg DMA/kg soil is converted to acid equivalent, it is 291 mg a.e./kg soil (i.e. Molar Mass Acid (221.0) / Molar Mass DMA (266.1) = 0.831. 0.831 x 350 = 291 mg a.e./kg soil).

4.3.12 Comment
The LD50 for the honey bee is inconsistent between PACR2005-01 and PACR2007-06. Please clarify.

Response
The LD50s for the honey bee in PACR2005-01 should have read as >83 µg a.e./bee (DMA) and >68 µg a.e./bee (EHE). The >100 µg a.i./bee for DMA and EHE are converted to acid equivalent. Molar mass EHE = 333.3, i.e. >100 µg a.i./bee is 0.831 x 100 = 83 µg a.e./bee for DMA and 0.663 x 100 = 66 µg a.e./bee for EHE.

4.3.13 Comment
PACR2007-06 does not mention the 2,4-D ester biotransformation to 2,4-D acid is rapid, with a half-life in natural waters of approximately six hours. As biotransformation of the ester is rapid in natural water (6.2 hour half-life for EHE), the toxicity for the ester form in freshwater fish should default to the acid toxicity for freshwater fish.

Response
Although a study does show the half-life of the EHE in natural waters is 6 hours, the fact remains that both the EHE and the BEE are considerably more acutely toxic than the acid and amines by two or three orders of magnitude. In acute tests with the EHE and the BEE, there does not appear to be much difference between static test toxicity results and flow through test results. With static tests, the ester concentrations decline over time, and acid concentrations increase as a result of ester transformation. With flow through tests, the ester concentrations are continuously maintained. Although the ester may transform rapidly, it does not appear to transform rapidly enough to reduce the toxicity of the ester form to that of the acid in static tests. Therefore,
esters can be considered to be present long enough to have a significantly greater toxic effect than the acid even if the half-life is only 6 hours. For the early life stage (embryo larval chronic) tests, which were 32 days in length, all the tests were performed under flow through conditions. The esters are about 3 to 4 orders of magnitude more toxic than the acid. However, even though the tests were static this may not have changed the result if most of the toxic effects occurred in the first 6 hours of the tests. The PMRA will reword its review as follows:

The toxicity of the technical esters to freshwater fish may have been limited by their very low solubility to virtual insolubility in water. 2,4-D esters biotransformation to 2,4-D acid is rapid with a half-life in natural waters of approximately 6 hours. Although the duration of the exposure of the esters is short, the available toxicity data for freshwater fish suggest it is sufficient time to have a significant toxic effect. This is indicated by the fact that the available static and flow through toxicity tests yielded toxicity values which are similar in magnitude. If the short duration of the esters in water was not sufficient to have a significant toxic effect then one would expect a significant difference between flow through and static toxicity tests.

4.3.14 Comment
The chronic and acute toxicity assessments should recognize that the evaluation of the toxicity of the technical esters to estuarine/marine fish was likely limited by the esters’ very low solubility to virtual insolubility in water. 2,4-D esters’ biotransformation to 2,4-D acid is rapid with a half-life in natural waters of approximately 6 hours.

Response
The assessments will be revised with an additional sentence for clarity:

Biotransformation of 2,4-D esters to 2,4-D acid is rapid with a half-life in natural waters of approximately 6 hours. Although the duration of the exposure is short, it may have sufficient time to have a significant toxic effect.

4.3.15 Comment
The product labels should include precautionary statements to reduce the risk of contamination to aquatic sites through surface runoff. In addition, statements should be added to 2,4-D product labels to mitigate the downward movement of these products in soil and, therefore, reduce groundwater contamination.

Response
Downward movement and runoff of 2,4-D is reduced by reducing the volume of water applied to the soil surface. As the 2,4-D transformation is primarily by microbial degradation, transformation occurs rapidly on the surface and in the upper microbially active part of the soil. If 2,4-D reaches a biological inert environment, its transformation rate is slowed. Label upgrades under the heading ENVIRONMENTAL HAZARDS indicate “2,4-D use may contaminate groundwater when soils are permeable or the water table is shallow and to avoid application when heavy rain is forecast.” Following these steps will mitigate groundwater contamination.
5.0 Comments with Respect to Value

5.1 Comment
The role of the amine salt needs clarification. With regards to foliar uptake into plants, additional information regarding neutralization of the acid and subsequent formation of a negatively charged ion dissolved once in the plant tissue should be included in the discussion. Also, the amine form efficacy statement is incomplete. It should state 2,4-D effectiveness is based on ~90% foliar uptake versus ~10% root uptake.

Response
The PMRA agrees that the comparison between amines and esters in PACR2007-06 was incomplete. Thus, the review will be revised as follows:

Herbicides containing 2,4-D are active in the acid form, but are formulated as amine salt or ester forms to enhance the ability of 2,4-D acid to enter into the plant. Plant roots most readily absorb the polar forms of 2,4-D (salt forms) and the leaves most readily absorb the non-polar forms of 2,4-D (the acid and ester forms). 2,4-D is translocated throughout the plant.

In 2,4-D herbicides, the parent acid binds to the herbicide target site within the plant and causes plant death, while the amine or ester parts do not have any direct role in herbicidal activity. Therefore, when assessing 2,4-D, the application rates were expressed in terms of the amount of acid equivalent per hectare (e.g. kg a.e./ha).

5.2 Comment
Tables 3.1.1 and 3.1.2 and Appendix I of PACR2007-06 present lists of the various registered products and details of ownership of the registration, product purity and form. Although Appendix I clearly indicates these details are as of 31 May 2005, it is a full two (2) years prior to the issuance of PACR2007-06. It is recommended that if such product listings are to be included in the final Re-evaluation Decision Document, that a contemporary (i.e. less than 6 months prior to publication) tabulation to registration details be captured.

Response
The risk assessments presented in PACR2007-06 were based on the uses as listed in Appendix II, which were registered as this active ingredient was being re-evaluated. It should be noted that while a number of products were discontinued during the re-evaluation period, the use profile of 2,4-D remained static. A complete listing of currently registered herbicides containing 2,4-D is available online in the PMRA’s Public Registry, under Product Information at www.pmra-arla.gc.ca/english/pubreg/pubreg-e.html.

5.3 Comment
With the large increase in seeded canola acres in western Canada over the past 10 years, 2,4-D has become a very important weed management tool for volunteer canola control in cereal crops such as wheat and barley.
Many of the common and heavily used herbicide groups in Canada (especially those in Group 2) have high incidences of resistant weeds. For example, Group 2 resistant kochia is a huge problem in western Canada, while Group 2 resistant redroot pigweed is a problem in eastern Canada. 2,4-D is an excellent resistance management tool as it can be used to control many Group 2 resistant weeds.

**Response**

2,4-D is used for the control of volunteer canola in cereal crops and kochia. It is also used to control Group-2 resistant weeds such as redroot pigweed. Control of volunteer canola in wheat, barley and rye is listed on product labels (i.e. 2,4-D Amine 600 Herbicide [PCP Registration Number 5931] and 2,4-D Amine 500 Herbicide [PCP Registration Number 9547]). Control of Group 2 resistant kochia is not presented on 2,4-D product labels, but control of kochia is included on several Commercial Class 2,4-D product labels. Moreover, control of redroot pigweed (including Group 2 resistant types) is claimed on the label of several Commercial Class products containing 2,4-D.

**5.4 Comment**

As proposed, it would be a very good idea to indicate a maximum application rate on the label of all 2,4-D products designed for non-cropland areas. The rate should be stated in litres of commercial product per hectare based on the product involved, and should not be stated in kilograms of acid equivalent (a.e.) per hectare. This way, applicators will not have to perform the conversion on their own to obtain the a.e. value.

**Response**

These changes in expression of maximum application rates of product will be reflected in the new labelling requirements. Registrants will therefore adjust their maximum product label rates of application so as to equal the rates of acid equivalent.

**5.5 Comment**

Fertilizer/pesticide combination products should be discontinued.

**Response**

Fertilizer/pesticide products are registered under the *Fertilizers Act* by the Canadian Food Inspection Agency. The Healthy Lawns website indicates that combined fertilizer/pesticide products (weed-and-feed type) should only be considered when a lawn has a nutrient deficiency and a widespread weed problem that cannot be controlled using other weed-control methods (e.g. hand weeding, spot spraying). New label upgrades will encourage spot treatments. The PMRA recognizes these products could be misused and continues to work with the Canadian Food Inspection Agency on the regulation of weed-and-feed products. The assessment for 2,4-D considered its use in fertilizers and found risks to be acceptable.
Appendix II  
Label Changes Required for Increased Protection to Human Health and the Environment

In addition to the statements already presented on the label, the following label statements must be added to the existing text.

1.0  Expression of the Guarantee—All Products

The guarantee statement on the labels of all products must be revised to specify the form of 2,4-D contained (i.e. one of the forms indicated in PACR2005-01, Table 2.6.1) and the proportion of 2,4-D acid equivalents. For example, for the DMA form, the guarantee should read: “2,4-D, present as the dimethylamine salt... y % a.e.” for solid products or “y g a.e./L” for liquid products where “y” is the equivalent concentration of 2,4-D as the acid. Note that the only form of 2,4-D isooctyl ester supported is the 2-ethylhexyl ester.

2.0  Human Toxicology Statements

Labels of Commercial Class products containing 2,4-D must include the following text (amendments have already been made to the labels of technical and manufacturing products).

For products containing acid and amine forms

**Toxicological Information**

2,4-D may cause severe irritation to the eyes.* Overexposure to 2,4-D may cause coughing, burning, dizziness or temporary loss of muscle coordination. Other possible effects of overexposure include fatigue, muscle weakness or nausea. Treat symptomatically.

* This statement may be modified by product-specific data.

For products containing the ester form

**Toxicological Information**

This product may cause mild irritation to the eyes.* Overexposure to 2,4-D may cause coughing, burning, dizziness or temporary loss of muscle coordination. Other possible effects of overexposure include fatigue, muscle weakness or nausea. Treat symptomatically.

* This statement may be modified by product-specific data.
3.0 Personal Protective Equipment and Restricted-Entry Intervals Relating to Occupational Exposure

The labels of all products containing the acid, DMA or EHE forms must contain the following statements in the PRECAUTIONS section:

**All Formulations—Application Using Handheld Equipment (all formulations)**
- Applicators must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
- Mixers/loaders/applicators using handheld equipment must wear a respirator if they will be handling more than 5 kg a.e. per day (sufficient to treat approximately 115 L/day at the highest rate of 0.0448 kg a.e./L).
- DO NOT handle more than 8 kg a.e. per day (sufficient to treat approximately 180 L/day at the highest rate of 0.0448 kg a.e./L)

**All Formulations—Aerial Application**
- Applicators must wear coveralls over a long-sleeved shirt and long pants. Chemical-resistant gloves must also be worn during clean-up and repair activities.
- No human flaggers are permitted.

**Liquid Formulations—All Scenarios**
- Mixers/loaders must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
- When handling more than 265 kg a.e. per day (approximately 120 ha at highest agricultural rate—2.24 kg a.e./ha), workers must also use a closed system.

**Liquid Formulations—Application Using Groundboom Equipment**
- Applicators must wear coveralls over a long-sleeved shirt and long pants. Chemical-resistant gloves must also be worn during clean-up and repair activities.

**Soluble Granule Formulations—Application Using Groundboom Equipment**
- Mixers/loaders must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
- Applicators must wear coveralls over a long-sleeved shirt and long pants. Chemical-resistant gloves must also be worn during clean-up and repair activities.
- When handling more than 300 kg a.e./day (approximately 135 ha at highest agricultural rate—2.24 kg a.e./ha), workers must also use a closed cab.

**Granular Formulations—All Scenarios**
Mixers/loaders must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

**Granular Formulation—Application Using Push Granular Spreaders**
Applicators must wear a long-sleeved shirt, long pants and chemical-resistant gloves.
Granular Formulation—Application Using Tractor-Drawn Granular Spreaders
• Persons handling the product must wear coveralls over a long-sleeved shirt, pants, shoes, socks and chemical-resistant gloves.

Granular Formulation—Application in Non-Cropland
Do not apply granules by hand.

Granular Formulation—Application in Non-Cropland Areas as a Soil Sterilant
• Persons handling the product must wear coveralls over a long-sleeved shirt, pants, shoes, socks and chemical-resistant gloves.
• Workers handling the product must not handle more than 1.50 kg a.e. per day (sufficient to treat approximately 755 m²/day at the highest rate of 0.225 kg a.e./100 m² or 6 boxes of product).

The labels of all products containing the IPA, TIPA or BEE forms must contain the following text in the PRECAUTIONS section:

Liquid Formulations—Ground and aerial
Closed mixing/loading systems are required.
• Mixers/loaders must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

Liquid Formulations—Aerial Application
• Applicators must wear coveralls over a long-sleeved shirt and long pants. Chemical-resistant gloves must also be worn during clean-up and repair activities.
• No human flaggers are permitted.

Liquid Formulations—Groundboom Equipment
• Applicators must wear coveralls over a long-sleeved shirt and long pants. Chemical-resistant gloves must also be worn during clean-up and repair activities.
• When handling more than 170 kg a.e. per day (approximately 75 ha at highest agricultural rate—2.24 kg a.e./ha), workers must also use a closed cab.

Liquid Formulations—Handheld Equipment
• Applicators must wear coveralls over a long-sleeved shirt, long pants, respirator and chemical-resistant gloves.

The labels of products containing the acid, DMA or EHE forms must contain the following statement under DIRECTIONS FOR USE:

• All liquid or soluble granule products, all crops—12-hour restricted-entry interval (REI)
• Alfalfa stand removal (fall application)—3-day REI
• Corn (sweet)—14-day REI for hand harvesting

The labels of products containing the IPA, TIPA or BEE forms must contain the following statement under DIRECTIONS FOR USE:
• All liquid or soluble granule products, all crops—12-hour REI
• Alfalfa stand removal (fall application)—13-day REI
• Corn (field)—3-day REI
• Established grass pastures, rangeland, perennial grassland in agricultural production—3-day REI
• Grass grown for seed—2-day REI
• Fallow land and crop stubble—3-day REI
• Non-cropland (annual and perennial weed control)—9-day REI for scouting by foot

4.0 Statements Related to Environmental Exposure

The following label statements must be included under ENVIRONMENTAL HAZARDS:

Toxic to small mammals, birds, aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

This product will harm other broadleaved plants in the vicinity of the treatment area. If applying this product using a handheld sprayer, do not directly spray or allow the spray to drift onto ornamentals or gardens.

Do not spray exposed roots of trees and ornamentals.

LEACHING

The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow.

RUNOFF

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

Avoid application of this product when heavy rain is forecast.

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

To prevent runoff from domestic uses avoid spraying on driveways, sidewalks or other hard surfaces. Do not irrigate within 24 hours after application.

The following label statements must be included under DIRECTIONS FOR USE:

DO NOT apply this product directly to freshwater habitats such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands, estuaries or marine habitats.

DO NOT contaminate irrigation/drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.
Field sprayer application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) coarse classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply when wind speed is greater than 16 km/h at flying height at the site of application. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) coarse classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Buffer Zones to Protect Sensitive Aquatic Habitat

Use of the following spray methods or equipment DO NOT require a buffer zone: hand-held or backpack sprayer and spot treatment.

The buffer zones specified in the tables below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Seasonal water bodies require buffer zones if there is water in them during application. Water bodies which do not fill on an annual basis need not be buffered.

BEFORE AERIAL APPLICATION TO FORESTS consult the most recent provincially approved topographic maps of the area to be treated (1:50 000) or more up-to-date information (e.g. GPS systems) to identify sensitive aquatic habitats. Sensitive aquatic habitats include:
(a) All running and standing water bodies, including impoundments, beaver ponds and bog ponds, that appear on the map or GPS system;
(b) Running and standing water bodies that do not appear on the map or GPS system, but are visible from the air.

Buffer Zones to Protect Sensitive Terrestrial Habitat

Use of the following spray methods or equipment DO NOT require a buffer zone: hand-held or backpack sprayer and spot treatment.

For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required; however, the best available application strategies that minimize off-site drift, including meteorological conditions (e.g. wind direction, low wind speed) and spray equipment (e.g. coarse droplet sizes, minimizing height above canopy), should be used. Applicators must, however, observe the specified buffer zones for protection of sensitive aquatic habitats. For the use of the herbicide in site preparation and conifer release in forestry, terrestrial buffer zones are not required.
The buffer zones specified in the tables below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands), and estuarine/marine habitats.

**Buffer Zones for 2,4-D Acid/Amine Derivatives for the Protection of Aquatic and Terrestrial Habitats**

<table>
<thead>
<tr>
<th>Method of Application</th>
<th>Crop</th>
<th>Buffer Zones (metres) Required for the Protection of:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Freshwater Habitat of Depths:</td>
<td>Estuarine/Marine Habitats of Depths:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less than 1 m</td>
<td>Greater than 1 m</td>
</tr>
<tr>
<td>Field sprayer*</td>
<td>Golf courses, turf</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Field crops (cereal grains, corn, grain and forage sorghum, asparagus, strawberries, raspberries)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Grasslands, fallow land and crop stubble, non-cropland (including rights-of-way** and brush control)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pastures, rangelands</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Forestry (site preparation)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
## Method of Application

<table>
<thead>
<tr>
<th>Crop</th>
<th>Buffer Zones (metres) Required for the Protection of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freshwater Habitat of Depths:</td>
</tr>
<tr>
<td></td>
<td>Less than 1 m</td>
</tr>
<tr>
<td>Aerial</td>
<td></td>
</tr>
<tr>
<td>Field crops (cereal grains, corn, grain and forage sorghum, alfalfa)</td>
<td>Fixed wing 1</td>
</tr>
<tr>
<td></td>
<td>Rotary wing 1</td>
</tr>
<tr>
<td>Grasslands, fallowland and crop stubble</td>
<td>Fixed wing 1</td>
</tr>
<tr>
<td></td>
<td>Rotary wing 1</td>
</tr>
<tr>
<td>Pastures, rangelands</td>
<td>Fixed wing 1</td>
</tr>
<tr>
<td></td>
<td>Rotary wing 1</td>
</tr>
<tr>
<td>Non-cropland (including rights-of-way** and brush control)</td>
<td>Fixed wing 1</td>
</tr>
<tr>
<td>2.24 kg a.e./ha</td>
<td>Rotary wing 1</td>
</tr>
<tr>
<td>4.48 kg a.e./ha</td>
<td>Fixed wing 2</td>
</tr>
<tr>
<td>Forestry (site preparation)</td>
<td>Rotary wing 1</td>
</tr>
<tr>
<td>2.4 kg a.e./ha</td>
<td>Fixed wing 15</td>
</tr>
<tr>
<td>3.1 kg a.e./ha</td>
<td>Rotary wing 5</td>
</tr>
<tr>
<td>4.48 kg a.e./ha</td>
<td>Fixed wing 30</td>
</tr>
<tr>
<td></td>
<td>Rotary wing 20</td>
</tr>
<tr>
<td>22.5 kg a.e./ha</td>
<td>Fixed wing 45</td>
</tr>
<tr>
<td></td>
<td>Rotary wing 30</td>
</tr>
</tbody>
</table>

NR = Not required*

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%.

** For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required.

† When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

‡ Terrestrial buffer zones are calculated using the HD₅₀ of the terrestrial plant species sensitivity distribution of the effect concentration 50% (EC₅₀) for all derivatives of 2,4-D.
## Buffer Zones for 2,4-D Ester Derivatives for the Protection of Aquatic and Terrestrial Habitats

<table>
<thead>
<tr>
<th>Method of Application</th>
<th>Crop</th>
<th>Buffer Zones (metres) Required for the Protection of:</th>
<th>Freshwater Habitat of Depths:</th>
<th>Estuarine/Marine Habitats of Depths:</th>
<th>Terrestrial Habitat†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Less than 1 m</td>
<td>Greater than 1 m</td>
<td>Less than 1 m</td>
</tr>
<tr>
<td>Aerial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Field sprayer*</td>
<td>Golf courses, turf</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Field crops (cereal grains, corn, grain and forage sorghum)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Grasslands, fallowland and crop stubble, non-cropland (including rights-of-way** and brush control)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pastures, rangelands</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Field crops (cereal grains, corn, grain and forage sorghum, alfalfa)</td>
<td>Fixed wing</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grasslands, fallowland and crop stubble</td>
<td>Fixed wing</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rotary wing</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pastures, rangelands</td>
<td>Fixed wing</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rotary wing</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Non-cropland (including rights-of-way** and brush control)</td>
<td>2.24 kg a.e./ha</td>
<td>Fixed wing</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>35</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4.48 kg a.e./ha</td>
<td>Fixed wing</td>
<td>125</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>50</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Forestry (site preparation)</td>
<td>2.4 kg a.e./ha</td>
<td>Fixed wing</td>
<td>175</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>95</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.1 kg a.e./ha</td>
<td>Fixed wing</td>
<td>225</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>125</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4.48 kg a.e./ha</td>
<td>Fixed wing</td>
<td>350</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotary wing</td>
<td>175</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>NR = Not required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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%.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>† When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>‡ Terrestrial buffer zones are calculated using the HD₅₀ of the terrestrial plant species sensitivity distribution of the EC₅₀ for all derivatives of 2,4-D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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%.

** For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required.

† When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

‡ Terrestrial buffer zones are calculated using the HD₅₀ of the terrestrial plant species sensitivity distribution of the EC₅₀ for all derivatives of 2,4-D.
5.0 Other Changes to Product Use to Increase Protection of Human Health and/or the Environment

5.1 Description of Registered Use Sites

If used on the label, the terms “non-cropland” and “industrial sites” must be defined specifically and indicated clearly on the label (e.g. for use on rights-of-way for transportation, rights-of-way for utility lines, in airports, in wastelands or in industrial parks).

5.2 Changes to Maximum Application Rates, Maximum Seasonal Application Rates, Maximum Number of Applications per Year or Maximum Amount of Pesticide to be Handled per Person per Day

<table>
<thead>
<tr>
<th>Site</th>
<th>Maximum Rate for a Single Application (g a.e. of 2,4-D/ha)</th>
<th>Cumulative Maximum Rate per Season (g a.e. of 2,4-D/ha)</th>
<th>Maximum Number of Applications per Year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine turf—granule, bar or stick products; 2,4-D alone or with other herbicides</td>
<td>1750</td>
<td>3500</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fine Turf—liquid products containing 2,4-D as the only herbicide</td>
<td>1550</td>
<td>3100</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fine Turf—liquid products containing 2,4-D and other herbicides</td>
<td>1250</td>
<td>2500</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Forest site preparation</td>
<td>4480</td>
<td>8960</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Grasses—established (forage/pastures/rangeland)</td>
<td>2240</td>
<td>4480</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Sorghum and millet (forage)</td>
<td>560</td>
<td>560</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Strawberries—postplantation</td>
<td>460</td>
<td>460</td>
<td>1</td>
<td>Rate for treatment at “dormance/after last picking” remains the same as current labels.</td>
</tr>
<tr>
<td>Raspberries—broadcast treatment</td>
<td>520</td>
<td>1040</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Raspberries—spot treatment</td>
<td>1250</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix II

#### Site Maximum Rate for a Single Application (g a.e. of 2,4-D/ha) Cumulative Maximum Rate per Season (g a.e. of 2,4-D/ha) Maximum Number of Applications per Year Comments

<table>
<thead>
<tr>
<th>Site</th>
<th>Maximum Rate for a Single Application</th>
<th>Cumulative Maximum Rate per Season</th>
<th>Maximum Number of Applications per Year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barley, rye and wheat—postemergence treatment in conventional tillage</td>
<td>880</td>
<td>880</td>
<td>1</td>
<td>Rate for pre-emergence treatment in minimum tillage system remains the same as current labels.</td>
</tr>
<tr>
<td>Corn (field)—post emergence (except for Jerusalem artichoke control)</td>
<td>600</td>
<td>600</td>
<td>1</td>
<td>For Jerusalem artichoke control, 2 postemergence applications of 325 g a.e. of 2,4-D/ha continue to be acceptable.</td>
</tr>
<tr>
<td>Fallow land and crop stubble</td>
<td>2240</td>
<td>4480</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Oats</td>
<td>Use no longer allowed</td>
<td></td>
<td></td>
<td>Use no longer allowed (see Note to CAPCO C94-08).</td>
</tr>
<tr>
<td>Non-cropland areas—annual and perennial weeds control</td>
<td>2240</td>
<td>4480</td>
<td>2</td>
<td>Hand-held equipment: maximum 2700 g a.e./day/person or 120 L/day/person at maximum rate</td>
</tr>
<tr>
<td>Non-cropland areas—woody plants control (Acid, DMA and EHE products)</td>
<td>4480</td>
<td>8960</td>
<td>2</td>
<td>Hand-held equipment: maximum 5000 g a.e./day/person without a respirator or 8000 g a.e./day/person with a respirator</td>
</tr>
<tr>
<td>Non-cropland areas—woody plants control (IPA, TIPA and BEE products)</td>
<td>4480</td>
<td>8960</td>
<td>2</td>
<td>Hand-held equipment: maximum 2700 g a.e./day/person with a respirator or 60 L/day/person at maximum rate</td>
</tr>
<tr>
<td>Tree and brush control—basal spray/frill/cut surface–stumps</td>
<td>1700 g a.e. / 1000 L diluent</td>
<td></td>
<td></td>
<td>Hand-held equipment: maximum 2700 g a.e./day/person</td>
</tr>
<tr>
<td>Site</td>
<td>Maximum Rate for a Single Application (g a.e. of 2,4-D/ha)</td>
<td>Cumulative Maximum Rate per Season (g a.e. of 2,4-D/ha)</td>
<td>Maximum Number of Applications per Year</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Tree and brush control— injection</td>
<td>1.32–2.64 g a.e. / injection site</td>
<td>—</td>
<td>—</td>
<td>Hand-held equipment: maximum 2700 g a.e./day/person</td>
</tr>
<tr>
<td>Vegetation control— granular soil sterilant</td>
<td>2250</td>
<td>2250</td>
<td>1</td>
<td>Handle maximum 1500 g a.e./day/person (6 boxes product); about 755m²/day at the highest rate</td>
</tr>
</tbody>
</table>

For non-cropland areas, if the rate of 2,4-D is given in terms of g a.e./L, the label should also specify a spray volume per hectare such as the maximum allowable rate per hectare is not exceeded. Note that changes are not required for the sites that are not listed in the table above.
References

A list of documents cited in this re-evaluation decision is included below. Additional references used in the re-evaluation of 2,4-D are available in the respective consultation and interim measures documents.

• Proposed Acceptability for Continuing Registration PACR2005-01, Re-evaluation of the Lawn and Turf Uses of (2,4-Dichlorophenoxy)acetic Acid[2,4-D]
• Re-evaluation Note REV2006-11, Lawn and Turf Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D]: Interim Measures.
• Proposed Acceptability for Continuing Registration PACR2007-06, Re-evaluation of the Agricultural, Forestry, Aquatic and Industrial Site Uses of (2,4-Dichlorophenoxy)acetic Acid [2,4-D].

This is limited to a subset of published studies including review articles and international regulatory documents. It is not an exhaustive listing of all published studies on 2,4-D. Other relevant information referenced within each of the published reviews and international documents were also considered in this re-evaluation, and these documents may be consulted for further reference listings. This list does not include references to the unpublished proprietary data used in this assessment. A complete list of references used in the evaluation of 2,4-D will be available upon request.


Sturtz, N, R. Duffard, et al. 2006. Detection of 2,4-D in rat milk of dams exposed during lactation and milk analysis of their major components. *Food and Chemical Toxicology*. 44(1):8–16.

