Health Canada | Santé Canada

Pest Management Regulatory Agency | Agence de réglementation de la lutte antiparasitaire

August 6, 2009

Ms. Meg Sears
RR 1, Box 9012
Dunrobin, ON K0A 1T0

Dear Ms. Sears:

Re: Notice of Objection - 2,4-dichlorophenozy acetic acid (2,4-D) RVD 2008-11

We have carefully reviewed your Notice of Objection, filed in August of 2008, regarding the Health Canada Pest Management Regulatory Agency (PMRA) decision to continue the registration of 2,4-D (RVD2008-11). We are aware of your long-standing interest in 2,4-D, and continue to make every effort to answer your questions and address your concerns.

Under the *Pest Control Products Act*, any person who believes there is a scientific basis for reconsideration of a decision to which subsection 28(1) applies can file a Notice of Objection within 60 days of the publication of the decision. Objections are expected to focus on the scientific basis of the decision related to health and environmental risks, the value of the pesticide and the need for this decision to be taken to an external panel of experts for consideration of the scientific argument presented in the Notice and to obtain advice to the Minister in that regard.

When a notice of objection is filed, a team of PMRA scientists, who were not involved in the original decision, is established. The team considers the scientific basis for the objection and determines if the criteria for the establishment of a review panel have been met.

Criteria for establishing a review panel include:

a. whether the information in the notice raises scientifically founded doubt as to the validity of the evaluation or re-evaluation of the health and environmental risks and the value of the pesticide; and
b. whether the advice of a panel of expert scientists would assist in addressing the objection.

.../2

Many of the concerns you raised in your objection were addressed during the extensive review and consultation process for the re-evaluation of 2,4-D, and in our previous communications with you over the years. Our team of PMRA scientists has carefully and extensively reviewed your questions and concerns, and has responded to each item separately in the attached document with information that was considered in the re-evaluation decision of 2,4-D. The team did not identify any scientifically founded doubt with respect to the validity of the re-evaluation in the information you provided in your objection. As a result this notice of objection does not fulfill the criteria to establish a review panel to reconsider the decision for continued registration of 2,4-D.

We trust that the information provided in the attached detailed response provides some clarity to the issues you raised. The PMRA continues to put human health and the environment at the forefront of our regulatory activities, and will only register products for which there is reasonable certainty that no harm will result from their use as directed, including 2,4-D.

Sincerely,

Marion Law
Chief Registrar
PEST MANAGEMENT REGULATORY AGENCY

Attachment:
Detailed Response to Notice of Objection

Attachment:
Sub. No. 2008-3120

Detailed Response to Notice of Objection – 2,4-dichlorophenoxy acetic acid (2,4-D) RVD2008-11

The notice of objection, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), by Ms. Meg Sears regarding the re-evaluation decision for 2,4-D has now been reviewed and assessed in accordance with the Act and Regulations.

The following information was received and reviewed in support of the notice of objection:

- Attachment to notice of objection (rationale)
- Sears, M., CR Walker, RHC van der Jagt and P Claman. 2006. Pesticide Assessment: Protecting Public Health on the Home Turf. *Paediatrics and Child Health* 11:229-234.
- June 18, 2008 email from the PMRA describing reports for various NOAELs.
- References annotated with abstracts.

Issues raised in the notice of objection are **bolded**, PMRA responses are not.

1. **Industry-supplied confidential animal toxicology reports under-estimate toxic effects. For example, symptoms such as excessive salivation or red material around eyes are not considered to be toxic effects. They should be - such symptoms are reported to occur in the majority of animals at doses well below the "No Observable Adverse Effect Level" (NOAEL). As well, evidence of toxicity (e.g. average body weight is half that of the control group) may not be statistically significant because either the experiments were poorly conducted so the scatter in the data is excessive, or too few animals were used. Only extreme toxicities (typically death) emerge as significant. In some key reports, toxic effects actually occurred at all doses. A particularly important point is that the chronic exposure NOAEL was inappropriately increased from 1 mg/kg bw/day (milligram per kilogram of body weight per day) to 5 mg/kg bw/day, after examination of new sections of old samples of rat kidneys. In addition, I bring to the attention of the PMRA a recent study in rats showing that exposure to as little as 10 mg/kg bw/day 2,4-D during the first post partum days produced changes in maternal behavior, serum prolactin and monoamine levels in the AcN of treated dams.[2] This is in contrast to the 12.5 or 25 mg/kg bw/day short term NOAELs incorporated in the 2,4-D re-assessment. Correction of these short term and chronic values should lead to recalculation of the acceptable human exposure, including an additional 10-fold factor for extrapolation from a "Lowest Observable Adverse Effect Level" (LOAEL) to a NOAEL. Proper**

incorporation of this new LOAEL into the assessment may preclude some or all uses of 2,4-D.

While industry does supply the confidential animal toxicology reports, it is important to note the PMRA reviews the industry data and makes its own decisions. PMRA's assessment includes the study data and statistical analysis and our decisions are independent of the decisions reached by industry.

Adverse vs. non-adverse effects:
Excessive salivation or red material around the eyes are not necessarily considered adverse effects. Excessive salivation can be the result of many things including a lack of palatability of the food with the test substance in it. Additionally, findings of excessive salivation or red material around the eyes were transient and, therefore, not considered adverse. A NOAEL is a no observed adverse effect level. In contrast, a NOEL, or the no observed effect level, is defined as the dose level at which not effects are observed regardless of whether they are adverse or not adverse and, therefore, would include these parameters. NOAELs are internationally recognized as the most appropriate endpoint for risk assessment. Subsequently, since it is the NOAEL that PMRA would use to determine endpoints, excessive salivation and/or red material around the eyes do not affect the determination of the endpoints. It should be noted that ophthalmic parameters were assessed in several of the studies as required by the OECD Guidelines. In the cases of 2,4-D EHE, 2,4-D DEA (which is being phased out of production based on the PMRA re-evaluation) and 2,4-D DMA bilateral retinal degeneration was observed in the 90-day rat studies. In the case of 2,4-D acid and sodium salt, similar findings were seen in the 2-year chronic rat study. It should be noted that these findings were either at or above the LOAEL for these studies. Therefore, adverse ophthalmic effects have been taken into account in the PMRA risk assessment.

Toxic effects:
The statement that "only extreme toxicities (typically death) emerge as significant" is not accurate. Many parameters were concluded to be adverse in the 2,4-D review such as decreased body weight, body weight gain, food consumption, liver effects, kidney effects, thyroid effects etc. In many cases, some or all of these effects were observed at doses lower than any mortalities and were the parameters used to determine the LOAEL.

PMRA does not rely on statistical significance as a sole means for determining the adversity of an observation. Biological significance (overall change, relative to control) as well as individual animal data are also taken into consideration. Please also note that the number of animals used in all the 2,4-D studies conducted did conform with the number of animals required for each type of study based on the OECD Guidelines.

Kidney pathology:
Kidney histopathology slides from the chronic 2-year rat study were re-assessed by an expert panel of pathologists at an independent institute. This professional peer review group determined that no adverse effects were seen in the kidney pathology at 5mg/kg bw/day. These slides were reassessed to verify the original findings, as a newer chronic

study did not show a similar effect at that dose level. Subsequently this information was assessed by the PMRA and, in the absence of other adverse effects at this dose level, the NOAEL for the chronic rat study was revised to 5 mg/kg bw/day.

2008 article:
In the paper "Effects of 2,4-dichlorophenoxyacetic acid on rat maternal behaviour" (Strutz et. al., 2008), the lowest dose tested in the cited paper is 15 mg/kg bw/day, which is 10 fold higher than the NOAEL in the chronic study, and does not identify effects at 10 mg/kg bw/day. The noted parameters (i.e., prolactin levels, monoamine levels in AcN and maternal behaviour) are not routinely assessed in short-term OECD Guideline studies, which use non-pregnant animals. However, observations such as maternal behavior or secondary effects related to other listed parameters would have been accounted for in several studies, including the 2-generation reproduction study within the toxicity database.

2. **There is no dispute that dioxins contaminate 2,4-D. There is an economic incentive to produce herbicides with higher levels of contamination because dioxins are produced in greater quantity at higher reactor temperatures; the same conditions under which production is more rapid and conversion more complete. Outstanding questions are the extent of contamination of products used in Canada, and the potential health impacts of dioxins with fewer than 4 chlorine atoms:**

    a. There is no dispute that dioxins contaminate 2,4-D. Indeed, according to Environment Canada, phenoxy herbicides are the largest source of lower chlorinated dioxins in the Canadian environment.[40]

Reference 40 does not state that phenoxy herbicides are the largest source of lower chlorinated dioxins in the Canadian environment. Reference 40 discusses sources of environmental contamination, the most significant dioxin sources being the wood preservative pentachlorophenol, municipal incinerators, and pulp and paper mills using chlorine for the bleaching process. Reference 40 does state that most of the sources produce complex mixtures containing both dioxins and furans, and gives 2,4-D as an example since it contains a mixture of dichloro-, trichloro- and tetrachloro-dioxins. While Reference 40 states that the second largest chemical source for dioxins is the herbicide 2,4-D, it also states that the dioxins contained in 2,4-D are not substituted in the 2, 3, 7 and 8 positions, and are considered to be relatively benign.

> **There is an economic incentive to produce herbicides with higher levels of contamination because dioxins are produced in greater quantity at higher reactor temperatures; the same conditions under which production is more rapid and conversion from feed stocks more complete. However, measures proposed by the PMRA to obtain contaminant information from the applicants will not be reliably informative because manufacturers monitor reactor temperature and dioxin contamination, so samples and data are readily selected by the applicants and may not be representative of products**

in use in Canada. The PMRA should review all production contaminant data from companies over the past perhaps 5 years, and also conduct its own tests of off-the-shelf phenoxy herbicides.

The manufacturing process of 2,4-D is confidential business information, thus the PMRA cannot discuss reaction temperatures and conditions. However, the statement "There is an economic incentive to produce herbicides with higher levels of contamination because dioxins are produced in greater quantity at higher reactor temperatures; the same conditions under which production is more rapid and conversion from feed stocks more complete." is not valid, since as you increase the percentage of dioxins you consequently decrease the percentage of the desired product. Thus there is an economic incentive to produce herbicides with low levels of contamination with a concurrent optimization of the active ingredient concentration. In addition, under Environment Canada's Toxic Substances Management Policy, registrants are required to work towards the virtual elimination of dioxins and furans from their products. As part of the re-evaluation of 2,4-D, registrants were required to submit recent analytical data for all identifiable dioxins and furans from at least five consecutive batches of technical grade product manufactured at each of the registered manufacturing sites. The PMRA will give consideration to your suggestion of reviewing contaminant data within the context of its enforcement and monitoring campaign. It will be evaluated in concert with other departmental priorities.

b. in published tests of immune suppression, the principle dioxin contaminant of 2,4-D was of potency similar to the most toxic dioxin. This is also the interpretation of the Agency for Toxic Substances and Disease Registry in the United States. The PMRA misrepresented the toxicity of 2,7-dichlorodibenzo-para-dioxin in the RVD2008-11.

The Agency for Toxic Substances and Disease Registry (ATSDR) cited two references with regard to dichlorodibenzo-para-dioxin immune suppression as the grounds for determining a positive result (Kramer et al., 1986 and Holsapple et al., 1986). As was indicated in the RVD2008-11, "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 dichlorodibenzo-para-dioxin 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 dichlorodibenzo-para-dioxin 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."

The ATSDR also indicated on page two, "2,3,7,8-TCDD is one the most toxic of the CDDs to mammals and has received the most attention. Thus, 2,3,7,8-TCDD serves as a prototype for the CDDs." Although 2,3,7,8-TCDD or other dioxins of concern may be present at levels below the production limit established by Health Canada, this level of contamination is so low that they would not be detected above background levels following use of 2,4-D products, and therefore would pose no additional health risk.

References:
Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs). Agency for Toxic Substances and Disease Registry.USA. 1998.

Kramer, C.M., J.J. Sando and M.P. Holsapple. 1986. Lack of direct effect of 2,3,7,8-tetrachlorodibenzo-P-dioxin (TCDD) on protein kinase C activity in EL4 cells. *Biochemical Biophysical Research Communications*. 140:267–272.

Holsapple, M.P., J.A. McCay, D.W. Barnes. 1986. Immunosuppression without liver induction by subchronic exposure to 2,7-dichlorodibenzo-p-dioxin in adult female B6C3F1 mice. *Toxicology and Applied Pharmacology*. 83:445–455.

c. Research is urgently needed on the health impacts of lower chlorinated dioxins, as well as their prevalence in the Canadian population and environment, as well as foods.

Health Canada will continue to monitor any new developments linked to this area.

3. Human epidemiology is not only afforded little weight in pesticide assessment, there is a major error in interpretation of a landmark study of non-Hodgkin lymphoma (nHL) in the RVD2008-11. This is a very serious, fundamental matter, calling into question competence in epidemiology and interpretation of statistical information. The 2006 study by Chiu et al.,[3] in concert with numerous other studies, clearly links phenoxy herbicides with the most intractable, most rapidly increasing type of nHL. The epidemiology literature is not comprehensively represented in the PMRA bibliography, and given the findings of the studies listed in successive publications there is good reason to believe that only studies that were pointed out by others are actually included in the list (pesticide proponents provided the literature referenced in the PACR2005-01 and studies pointed out by others were mentioned in successive documents). Similarly, other types of studies in the public, peer-reviewed literature were not systematically assembled or reviewed. Within the past few years, numerous studies (the preponderance of those reported) had significant findings of harms from phenoxy herbicides and 2,4-D in particular. Significant findings have been found for nHL, as well as for leukemia, breast cancer and brain tumours in people. Epidemiological studies should be used in pesticide assessment, or as they become available in subsequent adaptive management of the hypothesis that their use will not cause harm.

The statement that "pesticide proponents provided the literature referenced in the PACR2005-01" is incorrect. Most studies cited were the result of a PMRA conducted literature search. Also, as stated in the Bibliography section of PACR2005-01 and

PACR2007-06, "This is limited to a subset of published studies including reviewed 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 utilized in this assessment."

Chiu et al (2006) conducted a case-control study of agricultural pesticide use and non-Hodgkin lymphoma (NHL) in Nebraska, USA. Cases were 385 men and women identified through the Nebraska Lymphoma Study Group and area hospitals. Ninety percent of eligible cases participated in the study. Control subjects were randomly selected from the same geographical areas as cases and were frequently matched by sex, vital status, and age. Eighty seven percent of eligible controls (1432 of 1655) participated in the study. Pesticide exposure data was collected by self-report through telephone interviews. A subset of 175 cases was genotyped to determine the presence or absence of a specific chromosomal translocation (t(14;18)-positive/negative). Data on potential confounding factors including occupational history, obesity, and diet were collected as part of the study design but the influence of these factors on the reported findings were not explored in the analysis. Pesticide exposures were highly correlated between groups and the authors did not adjust for multiple pesticide exposures.

After adjusting for age, sex, type of respondent (direct or proxy interview), and family history of cancer, farmers who reported herbicide use (not specific to 2,4-D) had an increased risk of t(14;18)-positive NHL (OR=2.9, 95% CI: 1.1, 7.9) but not t(14;18)-negative NHL (OR=0.7, 95% CI: 0.3,1.2). While the authors reported risk estimates for specific chemical groups of pesticides, they specifically stated that they could not attribute the observed associations "to any particular chemical class of pesticides" owing to high correlations between pesticide groups. Relative to farmers who did not use pesticides, the odds of t(14;18)-positive NHL was greater among farmers not using phenoxy herbicides than among those who used phenoxy herbicides. The opposite would be expected if 2,4-D was a cause of NHL.

4. **The epidemiological, biochemical and toxicological literature is not systematically searched and synthesized to put together the scientific "puzzle-pieces." There is no systematic mechanism at the PMRA to do this. However, members of Canada's medical community who have done so have repeatedly expressed concerns that 2,4-D is persuasively linked to cancers, and reproductive, developmental and neurological problems. I was informed that when an epidemiological or other study comes to staff's attention, if the single study, in and of itself, is sufficient to overturn the decision then action would be taken. This is a very unlikely scenario.**

The PMRA conducts a systematic search of the scientific literature as part of the re-evaluation process. The PMRA examined epidemiological data in its review of 2,4-D. Some of these studies suggested weak associations, while others suggested no link between adverse health effects and the use of 2,4-D. Few, if any of these studies,

characterized exposure in the specific context of how the product was used. Using epidemiological studies in regulatory decision making is challenging in the absence of a direct measure of exposure.

Epidemiology studies that identify associations between the use of a product and a health effect are verified by conducting a toxicological evaluation that will determine the actual potential for cause and effect.

The PMRA undertakes these toxicity assessments to supplement information about associations that may be established by epidemiology studies.

The staff of the PMRA has access to peer reviewed science journals and do regularly search for new information. Additionally the new incident reporting program allows for certain studies of interest to be brought to PMRA's attention by outside parties.

5. **There is a disconnect between the animal toxicology studies and human observational studies, in that all animal studies are conducted at doses that are orders of magnitude higher than human exposures. PMRA staff repeat the simplistic, 16th century mantra favoured by the pesticide industry, that "the dose makes the poison." However, today we know that non-linear dose responses are common, and even exploited with some medications. Non-linear responses are common with chemicals that have hormonal or immune system effects (effects that are reported with 2,4-D), and in my brief survey of confidential test data non-linear responses were reported in animal toxicity studies (these were always dismissed as scatter in the data). The rationalization for using very high test doses is to elicit responses in greater numbers of animals, and even that lag times for delayed effects may be shortened at higher doses. However, it must be recognized that high-dose testing is an artefact of the assessment *system*. No tests will be conducted by the industry at doses that could not withstand application of the extrapolation factors, and remain above the human exposure estimates. Reverse engineering of experimental design in this context means that no testing will ever replicate levels of human exposure, and thus low dose effects will never be observed. This is why non-industry funded research is essential. The government should support university and governmental research into toxic effects of pesticides and other prevalent, potentially toxic chemicals.**

Paracelsus' statement concerning the dose making the poison does not necessarily imply that only a linear dose response is applicable. Hormonal and immune system effects can be triggered with exceptionally low dose levels. Genotoxic compounds also fit in to this category. It is correct that the current assessment system is designed to induce toxicological effects. That is how regulators, including the PMRA, are able to determine the potential dangers of a compound and then regulate accordingly by establishing an exposure level that is expected to be non-toxic. Testing at dose levels equivalent to human exposure levels would validate risk assessments and the PMRA continues to monitor research in this area. However, obtaining or requiring this information on a routine basis would be difficult, if not impossible, as there are many different exposure scenarios that would need to be tested and interpreted.

The scientists at the PMRA are very supportive of second and third party testing of toxic effects of chemicals. These studies further deepen the pool of information available to make sound regulatory decisions. The PMRA collaborates with other Branches of Health Canada as well as Environment Canada that assess potential toxicities of a wide range of chemicals including pesticides.

6. **Developmental and neurological toxicities have long been a concern, and the PMRA in its decision is calling for "confirmatory" data from a new study. The studies which are to be confirmed are poorly conducted and out of date (reports are from around 1990), and are not a sound basis for the decision to continue registration of 2,4-D. The design for the new study is presently being discussed. I am not an expert in assessing neurotoxicity endpoints in animals but am unaware of validation with endpoints such as autism or attention deficit. However, in addition to the measures mentioned in the recent work referenced in point 1 above, the following basic study-design recommendations are made to improve the proposed research in accordance with modern standards:**

    a. **extend the proposed study to 3 generations in total (two births), since previous research appeared to demonstrate effects at that stage;**

Recent research has indicated that mating animals beyond the first generation does not necessarily yield additional useful information (Janer et al., 2007). Instead of extending the study to include several generations, better use of the animals may be made through the assessment of additional endpoints of concern that traditionally have not been examined routinely in young animals, such as immunological measures and hormone levels. These assessments can provide for additional protection of human health by reducing uncertainty around the potential effect of environmental chemicals, including pesticides, on the developing human and subsequent consequences in the adult. Although the majority of cases indicate little benefit in testing beyond the first generation the use of "triggers" to extend the study beyond one generation when warranted, as is proposed by the International Life Sciences Institute (Cooper et al., 2006), can also be used and would allow for assessment of subsequent generations. PMRA scientists are currently participating in international workgroups that develop and enhance these protocols.

G. Janer, B.C. Hakkert, W. Slob, T. Vermeire, A.H. Piersma. (2007). A retrospective analysis of the two-generation study: What is the added value of the second generation? Reproductive Toxicology, 24:97-102.

R.L. Cooper, J.C. Lamb, S.M. Barlow, K. Bentley, A.M. Brady, N.G. Doerrer, D.L. Eisenbrandt, P.A. Fenner-Crisp, R.N. Hines, L.F.H. Irvine, C.A. Kimmel, H. Koeter, A.A. Li, S.L. Makris. (2006). A tiered approach to life stages testing for agricultural chemical safety assessment. Critical Reviews in Toxicology, 36:69-98.

    b. **include extra doses that are environmentally relevant;**

The doses selected for pesticide studies are conducted over a wide range of dose levels, including doses higher than those seen in the environment, in order to determine the doses at which adverse effects are seen as well as the dose levels below which *no* adverse effects occur. This in turn allows PMRA to determine those levels which are acceptable in the environment.

c. **use random methods to sample and pool production concentrates for testing, rather than using a highly purified form of 2,4-D that would be devoid of toxic contaminants;**

The purity of 2,4-D used in the studies, as is the case with all pesticides, is that which will be produced and used in the various end use products, thereby ensuring that the data accumulated on the pesticide is reflective of that which is actually available in the market.

d. blind researchers as much as possible as to treatment groups;

The OECD Guideline 426 for Developmental Neurotoxicity and the does not require a double-blind study design, however most companies currently employ this practice.

e. power the experiment to detect differences in readily measured parameters such as feed consumption and body weight;

OECD study guidelines are designed with an adequate number of animals to detect differences in the aforementioned parameters. In the case of reproduction studies, 20 animals per sex per dose are employed to elucidate potential effects that occur in reproduction studies.

f. analyse all feeds and used bedding to ensure that they are not inappropriately contaminated with 2,4-D, breakdown products or contaminants, or with other materials that may affect the outcome of the experiments (recent research has shown that animal feeds may skew results of toxicology experiments when endocrine effects are under investigation); and

In accordance with the Good Laboratory Practice Guidelines and OECD Guidelines, all feed must be analysed for contaminants that may affect the outcome of the studies conducted. Bedding is purchased from reputable suppliers who ensure the quality of the product to be suitable for laboratory research.

g. **analyse data and experimental standards independently.**

PMRA conducts an independent assessment of the study data including statistical analysis where appropriate.

7. **Clearly the 2,4-D information within the Agency is in disarray. Visits to the Reading Room were very informative. PMRA staff members were uniformly welcoming and appeared to be very cooperative. However, staff has yet to provide me with a single, clear bibliography of reports considered during the reassessment. Most recently, two bibliographies were provided that between them purportedly include all references. One list includes five partial references (journal page numbers only – no authors or titles) that were pointed out to the PMRA following publication of the decision. In general references have no consistent format and many are incomplete; indeed, many entries are unidentifiable due to missing information. During the second day in the Reading Room, when the studies were finally on the computer, some key, large electronic documents were not searchable. Thus searches for keywords such as "dioxin" or "child" were not comprehensive.**

In 2007, PMRA initiated a Reading Room Pilot to obtain feedback on the functionality of the Reading Room. In light of the feedback provided by the participants, the PMRA will be exploring options to enhance the user experience of the Reading Room. A *Response to the Reading Room Pilot Report* is presently being developed and will be published on Health Canada's website once completed. The comments raised in the objection relating to the Reading Room are being taken into consideration in developing the response.

8. **Making the PMRA Data Evaluation Reports (DERs) or the equivalent available was a key recommendation of the Reading Room Pilot Project, but this has not yet been acted upon. They should be publicly available as they would allow one to discern the logic and decision-points of the assessment process.**

As indicated above, a *Response to the Reading Room Pilot* is presently being developed. The PMRA is exploring options regarding the type of information made available in the Reading Room to provide greater transparency concerning the data and interpretations underlying PMRA's regulatory decisions. The comments raised in the objection relating to the Reading Room are being taken also into consideration.

9. **Research involving mixtures of pesticides is allotted minimal if any relevance, despite the fact that 2,4-D is almost always used in mixtures (a single one-pesticide product is registered), and that all products for turf (where the largest number of people are exposed) are mixtures. The PCPA requires cumulative assessment of pesticides with common mechanisms of toxicity, but phenoxy herbicides were not assessed in this manner. Pesticide assessment should take into account the way the material is used, not only in terms of application methods, but also other pesticides plus ingredients that may affect penetration/absorption, metabolism and toxicity.**

Pesticide mixtures or "end use products" are evaluated by PMRA in the form of acute studies and the results for these studies determines the hazard statements on the individual product labels for each end use product. Acute studies for end use products containing 2,4-D show they are less toxic to mammals than the full strength technical grade active.

The PCPA requires that the PMRA consider the cumulative exposure to pesticides that have a common mechanism of toxicity. In 2001, the PMRA published guidance on the approach to cumulative assessment in "Science Policy Notice SPN2001-01 Guidance for Identifying Pesticides that Have a Common Mechanism of Toxicity for Human Health Risk Assessment". The PMRA's approach closely parallels that of the US EPA who identified four classes of pesticides that are subject to cumulative assessment by virtue of a common mechanism of toxicity. These classes include Organophosphates, N-methyl carbamates, triazines andchloroactanilides. At this time there is no data with regard to common mechanisms for toxicity for 2,4-D and other phenoxy herbicides. As a result a cumulative assessment is not possible.

Childhood Cancer

In the PACR2005-01, the Scientific Advisory Committee recommended that childhood cancer related to exposure to 2,4-D merited more study. There has been no evidence of this work by the PMRA. However, in 2007 Dr. Infante-Rivard *et al.* published "Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review," stating "one can confidently state that there is at least some association between pesticide exposure and childhood cancer.[34] However, an unambiguous mechanistic cause-and-effect relationship between pesticide exposure and childhood cancer was not demonstrated in these studies, and modifying factors such as genetic predisposition, rarely considered in the reviewed studies, likely play an important role. While the time window of exposure may be a crucial determinant for biological effects associated with pesticide exposure on children, studies have not contributed definitive information on the most vulnerable period. Accurate exposure assessment remains a challenge; future epidemiological studies need to assess gene-environment interactions and use improved exposure measures, including separate parental interviews, specific pesticide exposure questions, and semiquantitative exposure measures that can be used to confirm information obtained through questionnaires." In this situation, it is the role of the PMRA to minimize children's exposures to the pesticides examined in such studies, and 2,4-D is very commonly used.

As noted in the REV 2006-11, the issue of childhood cancers and any potential relationship with pesticide exposures in general is much broader than the re-evaluation of 2,4-D, in that available data for consideration may or may not include 2,4-D exposure. Based on the overall analysis of the toxicity and epidemiology data for 2,4-D, the PMRA does not consider 2,4-D to be carcinogenic. This is consistent with the 2,4-D assessment by other regulatory authorities including the US EPA, the European Commission. As well, in the absence of any cancer findings in the animal toxicity data, a quantitative cancer risk assessment for 2,4-D is not required, nor is not possible. As noted by the commentator, a more recent study by researchers at McGill University (2007) reported

potential association between childhood cancers and pesticides in general. As individual pesticides have very different toxicity profiles, broad associations such as that reported in the noted study are very difficult to interpret and integrate into regulatory decisions for individual compounds. Epidemiological studies that properly characterize exposure to a given pesticide are most useful in informing the regulatory decisions making process.

For the reasons provided in the foregoing responses, it has been determined that the information provided in support of the objection does not meet the requirement of identifying issues in relation to the regulatory decision that warrant the establishment of a review panel to provide scientific advice. As a consequence, a review panel will not be established to reconsider the registration decision in response to this request.