PRELIMINARY NOTICE CONCERNING THE SELECTION OF AN ADULTICIDE FOR THE CONTROL OF MOSQUITOES TO PREVENT THE TRANSMISSION OF WEST NILE VIRUS IN QUEBEC AND ELSEWHERE IN CANADA

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1. INTRODUCTION

In the event that West Nile virus (WNV) enters Canada, the control of the principal vector would be one of the key components of the efforts to limit the spread of this virus. At the present time, it appears that mosquitoes are the primary vector of WNV to humans and other animals.

The use of insecticides for this purpose is not without certain human health risks. For that reason, it is critical to select the product that offers the highest level of safety, both for the public and for workers who apply the treatments.

To determine what adulticide offers the highest level of safety, we evaluate the principal toxicity indices of the potential products identified for this type of work namely malathion, resmethrin, permethrin, propoxur and dichlorvos.

Given the lead time required to draft this notice, we focussed primarily on the most recent studies and those that most effectively met the new toxicity assessment requirements.

In order to take account of the most recent data concerning the inherent toxicity of malathion, our evaluation is based primarily on two documents: the most recent revision to the preliminary risk assessment for the eligibility of the product for reregistration by the United States Environmental Protection Agency (EPA) and the most recent toxicological and environmental assessment document produced by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Committee on Pesticide Residues.

In addition to the toxicological data specific to malathion, we also present a summary of the principal data for malaoxon, the metabolite primarily responsible for the toxicity of malathion.

The data concerning pyrethroids (resmethrin and permethrin) are more limited because these products are not currently considered priorities for toxicological reassessment. The data presented comes largely from the evaluations conducted by the World Health Organization.

In the case of propoxur and dichlorvos, the data are mainly drawn from decision documents of the U.S. EPA.

On the basis of a comparison of the available toxicological data, we were able to recommend an adulticide for control of mosquitoes. In our view, this recommendation will make it possible to ensure greater safety of mosquito control operations, should such a need arise.

2. TOXICITY PROFILE OF MALATHION

2.1 Acute toxicity

Malathion exhibits low acute toxicity via the oral, dermal and inhalation routes (Toxicity Category III or IV of the classification of the U.S. *Federal Insecticide, Fungicide and Rodenticide Act*). The product exhibits only slight eye and dermal irritation and is not dermally sensitizing. The principal acute toxicity indices of malathion are presented in Table 3.

A number of earlier studies indicate higher toxicity levels. However, the results of these studies were significantly affected by impurities present in the malathion. For purposes of comparison, the LD_{50} values for these impurities in rats after oral administration of malathion are: isomalathion, 89-120 mg/kg; 0,0,S-trimethylphosphorodithioate, 450-660 mg/kg; *O,S,S*-trimethyl phosphorodithioate, 26-110 mg/kg and *O,S,S*-trimethyl phosphorothioate, 47-260 mg/kg (IPCS, 1997).

Moreover, some data indicate that malaoxon, the active cholinesterase (ChE) inhibiting metabolite of malathion, is 10 to 30 times more toxic than malathion. Table 1 below presents the results of the few studies available in the literature.

Table 1. Acute toxicity of malaoxon

Test and species	Results	Date	Toxicity Category (FIFRA)
Acute Oral – Rat	215 mg/kg	1980	II
Intraperitoneal – Rat	~25 mg/kg	1967	
Acute Oral - Rat	142 - 175	1966	II

2.2 Subchronic toxicity

In subchronic studies with malathion, plasma and red blood cell (RBC) ChE inhibition was exhibited at the lowest observed adverse effect level (LOAEL) in rabbits, following dermal exposure (300 mg/kg/day for 21 days) and in rats following inhalation exposure (0.1 mg/L) for 90 days. At the dose of 300 mg/kg/day, brain ChE inhibition was observed in female rabbits. Brain ChE inhibition was also observed at in both species at the highest (unspecified) doses tested. Clinical signs or other treatment-related effects were not observed in dermally treated rabbits. However, microscopic lesions of the nasal cavity and larynx were observed in rats following inhalation exposure.

2.3 Chronic toxicity and carcinogenicity

The U.S. Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of malathion and malaoxon in 1999-2000. Malathion is classified as exhibiting suggestive evidence of carcinogenicity, although it is not sufficient to assess human carcinogenic potential. This classification is based on the following factors:

- occurrence of liver tumours in male and female mice and in female rats only at excessive doses;
- the presence of a few rare tumours in rats (oral palate mucosa in females and nasal respiratory epithelium in both sexes). With the exception of one nasal and one oral tumour in female rats, all other tumour types occurred at excessive doses or were unrelated to treatment with malathion;
- the evidence for mutagenicity is not supportive of a mutagenic concern in carcinogenicity of malathion.
- malaoxon was not carcinogenic in rats.

The chronic toxicity and carcinogenicity profiles of malathion and malaoxon are presented in Table 3.

2.4 Developmental effects

In rabbits, a slight increase in the mean incidence of unimplanted fertilized eggs in dams was noted at 50 mg/kg/day, at which maternal toxicity was also observed. No developmental effects were noted in rats at the highest dose tested (800 mg/kg/day). Maternal toxicity (cholinergic signs and reduced mean body weights) were observed in both species.

A summary of the developmental effects is presented in Table 3.

2.5 Reproductive effects

Malathion did not induce reproductive toxicity in rats at the highest dose tested.

2.6 Mutagenicity

Genetic toxicology studies with malathion indicate that the product does not cause gene mutations in bacteria or unscheduled DNA synthesis in cultured rat hepatocytes. Similarly, malathion is not clastogenic up to doses that showed clear cytotoxicity for the target tissue *in vivo.* According to the U.S. Cancer Assessment Review Committee, the positive *in vivo* and *in vitro* findings in the literature should be interpreted with caution since positive results were seen at cytotoxic doses and/or the types of induced aberrations were not consistent with cell survival. The Committee concludes that the weight of the evidence supports neither a mutagenic hazard nor a role for mutagenicity in the potential carcinogenicity of malathion.

According to the studies, malaoxon is not mutagenic in bacteria but showed positive results in gene mutation assays with metabolic activation. This product was not clastogenic in cultured hamster ovary cells. However, the findings from the mouse lymphoma assay suggest that malaoxon may induce both gene mutations and chromosome aberrations.

A summary of the mutagenicity studies is presented in Table 3.

2.7 Neurotoxicity study

The neurotoxicity of malathion was evaluated in acute and subchronic neurotoxicity studies in rats and in an acute delayed neurotoxicity study in chickens. These studies were found to be acceptable by the U.S. EPA, but a developmental neurotoxicity study is required in order to meet the agency's new requirements.

The acute delayed neurotoxicity study in chickens did not reveal any treatment-related findings. However, in acute and subchronic neurotoxicity studies in rats, neurotoxic effects, including clinical signs and inhibition of RBC, plasma and brain ChE activity, were observed.

2.8 Metabolism

In rats, malathion is excreted primarily in the urine (80–90%) and feces in the first 24 hours following exposure. Malathion did not bioaccumulate in the tissues or organs. The main metabolites observed in urine are malathion in the form of monoacids and dicarboxylic acid (80% of the radio-labelled malathion measured). Between 4 and 5% of the administered dose is converted to malaoxon.

2.9 Cases of human exposure

In the United States, there are several sources of information on pesticide exposures and poisonings:

•OPP Incident Data System (IDS)
•Poison Control Centers (PCC)
•California Department of Pesticide Regulation
•National Pesticide Telecommunication Network (NPTN)

Close to 70 separate incidents have been reported under IDS, some of which involving multiple individuals. There were a total of 10,637 malathion cases in the PCC data base, of which 564 were occupational exposure involving malathion alone. There were 5,757 adult non-occupational exposures and another 3,371 exposures reported in children under age 6. According to the California Illness Surveillance Program (1982 through 1995), malathion was responsible for the

health effects seen in 395 cases, causing it to be ranked sixth among the causes of systemic poisoning in California between 1982 and 1994. It was determined, however, that the single largest cause of exposure was broken or leaking packaging of the insecticide. Exposure to malathion as a result of insecticide drift (i.e., movement of the product outside targeted treatment areas) was the second most common cause.

In Florida during 1998, malathion was applied to control the citrus pest, the Medfly, in an area with 132,000 residents. There were at least 34 probable poisonings and 89 possible poisonings resulting from this application. Most of the effects were sensitization or irritant/allergic reactions to malathion.

From April, 1 1995 to March 31, 1998, the NPTN received 95 reports of incidents in humans alleging adverse health effects from malathion. The most common complaints were related to odours from insecticide drift or accidental spills that resulted in minor symptoms, such as headache, nausea and respiratory problems.

2.10 Risk assessment

The Office of Prevention, Pesticides and Toxic Substances of the U.S. EPA conducted a preliminary assessment of the risks of exposure to malathion. A total of 16 exposure scenarios were subject to a risk assessment, including ULV (ultra low volume) aerial and ground applications of malathion to control mosquitoes. The risks of exposure following an application were assessed for adults and children of walking age (i.e., 1 to 6 years old).

Several parameters, such as insecticide residue following aerial application, had to be modeled due to the lack of field data. Moreover, for the aerial application, the wind used by the authors is 2 miles/hour (3,2 km/hour). However, it is important to note that this value is much lower comparatively at these normally used in operating conditions (see Florida White paper for Control of Mosquitoes http://www.ifas.ufl.edu/~VEROWEB/WHITEP/toc.htm, Chapter 6).

According to the risk estimates, the aggregate risks of exposure (food + dermal + inhalation) of residents following an aerial application to control insects do not exceed the level of concern defined by the U.S. EPA, both for children and adults. The Agency stresses that the exposure scenario retained is conservative. The same conclusion was reached for the ground application scenario. However, the aggregate risk index for dermal and inhalation exposure could exceed the Agency's level of concern for several residential utilization or residential post application exposure scenarios (adults and children 1-6 years old). Thus, all residential use combined with uses designed to control WNV could significantly increase the risk of exposure to malathion. The assessment of the combined risks of occupational dermal and inhalation exposure revealed a potential risk for only one scenario involving the control of mosquitoes namely, the tasks of mixing and loading products for ULV aerial application. The authors note, however, that these risks should be low because the calculated risk index is very close to the safe level defined by the U.S. EPA.

The risk estimates take account of the use of malathion only. Since the organophosphates share a common mechanism of toxicity, namely ChE inhibition, it is possible that the level of risk increases with concomitant use of several organophosphates.

3. TOXICITY PROFILE OF PERMETHRIN

3.1 Acute toxicity

In acute toxicity tests with various animal species, permethrin exhibited low acute toxicity although the LD_{50} values vary considerably depending on the vehicle used (water, oil, etc.) and the isomeric ratio (*cis:trans*). For example, the LD_{50} of permethrin is almost 10 times lower when the product is administered in corn oil or olive oil rather than with water, likely due to enhanced absorption. *Cis*-permethrin is more toxic than *trans*-permethrin to rats and mice. None of the metabolites of permethrin shows a higher acute toxicity than permethrin itself.

In studies with rabbits, permethrin caused a mild primary irritation but did not cause a photochemical irritation reaction. It also caused minimal eye irritation. In studies with guinea pigs, this insecticide did not cause a sensitization reaction.

Pyrethroids can induce paresthesia, which is the effect most often described following dermal exposure to these products. The face is most often affected, although other parts of the body can also be affected, particularly areas having a high density of nerve endings. The most commonly reported symptoms are burning, tingling, itching and numbness. These symptoms are due to transitory stimulation of peripheral sensory nerves and do not constitute systemic toxic effects. The reaction occurs within 1 to 2 hours of exposure and can last more than 24 hours. It disappears spontaneously without treatment and has no known long-term effects.

3.2 Subchronic toxicity

Oral subchronic toxicity studies of permethrin have been performed in rats and mice, at dose levels up to 10,000 mg/kg, for periods of 14 to 26 weeks. At the highest dose, an increase in liver/body weight ratio, hypertrophy of the liver and clinical signs of poisoning, such as tremor, were observed. The no-observed-effects levels (NOEL) in rats ranged from 70 mg/kg diet in studies lasting 90 and 180 days to 150 mg/kg diet in a 180-day study.

NOEL values in dogs range from 50 to 100 mg/kg body weight for studies conducted over a 3-month period.

A summary of the subchronic effects is presented in Table 3.

3.3 Chronic toxicity and carcinogenicity

In long-term studies in mice and rats, an increase in liver weight was found which was likely associated with an induction of the liver microsomal enzyme system.

The NOEL in a 2-year study using rats was 5 mg/kg body weight. A similar NOEL value has been determined in dogs.

According to the results of several long-term studies using mice, it appears that permethrin could induce pulmonary tumours in some species of mice. These effects were observed at the highest dose (5 g/kg diet) and in females only. Oncogenic effects were not observed in rats.

The chronic toxicity profile of permethrin is presented in Table 3.

3.4 Developmental effects

In a study in which pregnant mice were orally administered permethrin at dose levels of 0 to 150 mg/kg body weight, from day 7 to 12 of gestation, neither the number of implantation sites nor the litter size was adversely affected. There were no teratogenic effects associated with permethrin in this study.

In other studies, rats were orally administered dose levels of between 22.5 and 225 mg/kg. Based on the results reported, permethrin does not appear to present a teratogenic or lethal hazard to the fetus.

In studies on rabbits, a dose level that was toxic to the dams (1,800 mg/kg body weight) was not teratogenic. However, at dose levels of 1,200 and 1,800 mg/kg, permethrin showed embryotoxic potential.

3.5 Reproductive effects

Several reproduction studies have been performed in rats in which animals were administered dose levels of between 20 and 4,000 mg/kg diet. All of the studies indicated that permethrin has no toxic effect on reproduction in rats.

3.6 Mutagenicity

In studies on rats and mice, permethrin was shown to be non-mutagenic. Similar results were observed in *in vitro* studies.

3.7 Neurotoxicity study

When administered to rats at very high dose levels (6,000 to 7,000 mg/kg diet), permethrin induced lesions of the sciatic nerve in one study, but a second study did not confirm this effect. Permethrin did not cause delayed neurotoxicity in hens.

3.8 Metabolism

Permethrin (*cis* and *trans* isomer) administered orally to rats is rapidly metabolized and almost completely excreted within a few days. It is excreted primarily in the urine and the major metabolite of the acid moiety, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid, is eliminated conjugated with glucuronic acid. In volunteers, depending on the isomer administered, up to 39% of the administered dose was excreted as 3(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid. The major metabolites from the alcohol moiety are 3-(4'-hydroxyphenoxy) benzoic acid sulfate and 3-phenoxybenzoic acid in free and conjugate form. Dermal absorption is estimated at only 2%.

3.9 Cases of human exposure

According to the WHO, although permethrin has been used for many years, there have been no reports of significant adverse effects following human exposure. Nonetheless, it recommends pursuing observations on this type of exposure. Some data indicate that permethrin could cause numbness, itching, tingling or burning of the skin. There appears to be no reported cases of systemic poisoning in humans.

3.10 Risk assessment

To date, we have been unable to obtain the data required to conduct the same type of risk assessment as for malathion. This analysis will be conducted at a later date if possible. However, the history of the use of permethrin and the few reported cases of poisoning following intensive and varied use, lead us to believe that the health risks of this product are low.

4. TOXICITY PROFILE OF RESMETHRIN

Resmethrin is a racemic mixture of 4 optical isomers: [1R, *trans*]-, [1R, *cis*]-, [1S, *trans*]-, [1S, *trans*]-. The composition ratio in technical products is roughly 4:1:4:1. The [1R, *trans*]- isomer is called bioresmethrin and the [1R, *cis*]- isomer is cismethrin. Among the isomers, the [1R, *trans*]- isomer has the highest insecticidal activity followed by the [1R, *cis*]- isomer. Unless otherwise indicated, the studies reported in this document are primarily for the technical product.

4.1 Acute toxicity

Resmethrin exhibits low acute toxicity via the oral, dermal and inhalation routes, as shown in Table 3, which summarizes the various indicators of toxicity (toxicity class, lethal dose and lethal concentration). The product is not considered to be an irritant to the eyes or skin and does not cause sensitization reactions in guinea pigs or New Zealand white rabbits.

No data have been reported on the toxicity of resmethrin for humans, but the signs of acute poisoning by this type of product at high dose levels in animals include: progressive development of slight body tremors, convulsive twitching of the dorsal muscles, hyperexcitability or hyperactivity, and convulsions.
The acute oral and intraperitoneal toxicity of several metabolites (chrysanthemic acid (CA), 5-benzyl-3-furylmethyl alcohol (BFA), 5-benzyl-furancarboxylic acid) has been studied in rats and mice. CA and BFA were more toxic than the parent compound, although the symptoms of toxicity were different. The acute toxicity (oral LD_{50}) of the metabolites in rats ranged from 997 to > 4,640 mg/kg, which is within the same range of acute toxicity as the parent compound.

It is theoretically possible that resmethrin can cause paresthesia; however, we did not find any documented cases of this condition associated with exposure to resmethrin.

4.2 Subchronic toxicity

In a 90-day dietary study using rats, the no-observed adverse effect level (NOAEL) for resmethrin and bioresmethrin was 66 and 33 mg/kg body weight per day, respectively. The NOAEL was 80 mg/kg body weight per day in a 90-day study in dogs.

In inhalation studies in rats and mice exposed to [1R, *trans*, *cis*]-resmethrin at concentrations of 0, 23, 47 or 210 mg/m^3 for 4 h/day, 5 days/week over one month, no toxic effects were observed on behaviour, food intake, hematology, clinical biochemistry, mortality or histopathology. In another study involving rats but for a longer period of exposure (i.e., exposure every 6 h each day, 6 days per week, over a period of 90 days), minor effects, such as changes to some chemical parameters and signs of irritation, were observed at the intermediate dose of 300 mg/m^3. At the highest dose of 1,000 mg/m^3, more significant effects were observed, but these were reversible during the recovery period. The NOEL for this study was 100 mg/m^3.

4.3 Chronic toxicity and carcinogenicity

In a chronic toxicity study in rats, an increase in liver size was found at the lowest dose tested (25 mg/kg/day). An increase in liver weight and pathological lesions of the liver were also observed at the intermediate dose of 125 mg/kg/day. These liver effects were also found at the highest dose administered (250 mg/kg/day), along with an increase in thyroid gland size and thyroid cysts. These thyroid effects were not reproduced in any other study.

In studies in which [1R, *trans*, *cis*]-resmethrin was fed to rats at dietary levels of 500, 1,500 or 5,000 mg/kg for 24 weeks, toxic symptoms, such as tremors, decreased body weight, increased liver and kidney weights and an increase in alkaline phosphatase activity, were observed at the maximum dose only. The NOEL was 77.7 mg/kg/day for males and 86.6 mg/kg/day for females, or the intermediate dose. In a two-year study in rats using similar dose rates, exposure caused systemic effects but not carcinogenicity. In dogs that were administered doses of 10, 30 or 300 mg/kg body weight for 6 months, the NOEL was 10 mg/kg per day. Increased liver weights were noted at the highest dose.

In an oncogenicity study in which resmethrin was fed to rats at dosage levels of 500 to 5,000 mg/kg in the diet over a 112-week period, no carcinogenic effect was observed. The NOEL of 500 mg/kg for toxic effects was also the lowest-observed-effect-level (LOEL) for hypertrophy of hepatocytes, which was not considered a definite toxic response. In mice fed resmethrin at dosage levels ranging from 250 to 1,000 mg/kg diet for an 85-week period, no carcinogenic effect was observed at the various doses tested.

4.4 Developmental effects

In a teratogenicity study in which pregnant rats were administered resmethrin in the diet at concentrations of 188 or 1,500 mg/kg from day 6 to 16 of gestation, no abnormalities of fetal skeletons or soft tissues were observed, though mortality, tremors and decreased food and water consumption were observed at the highest dose. In another study, in which resmethrin was administered to rats by gavage at dose levels up to 80 mg/kg/day, no teratogenic effects were observed. However, fetotoxicity was observed at the intermediate dose level of 40 mg/kg/day. In rabbits, dose levels of up to 100 mg/kg/day did not have teratogenic effects. When [1R,*trans*, *cis*]-resmethrin is administered orally to mice or rats during gestation at dose levels of 100 mg/kg/day and 50 mg/kg/day respectively, no toxic effects, such as spontaneous abortion, resorption of fetuses or embryos, external or skeletal abnormalities of pups or abnormalities in growth or organ differentiation, were observed.

4.5 Reproductive effects

A 3-generation study on the toxic effects of resmethrin on reproduction in rats revealed statistically significant effects of treatment on the number of stillborn pups per litter and on weight gains of pups during weaning. The lowest dose level that caused an effect was 25 mg/kg/day, the lowest level tested. This study, considered to be of high quality, was used to determine the reference dose level of 0.03 mg/kg/day.

4.6 Mutagenicity

Various species of microorganisms (e.g., *Saccharomyces cerevisiae*, *Salmonella typhimurium*, *Escherichia coli)* were used to evaluate the mutagenic potential of resmethrin. The compound was tested in the absence or presence of metabolic activators, namely liver microsomal enzyme preparations, and was not mutagenic to any of the indicator organisms used in the tests. Tests to study point/gene mutations in prokaryotes or eukaryotes, and chromosomal effects in hamster ovary cells, mouse bone marrow and cardiac blood cells of the mouse were all negative.

4.7 Neurotoxicity study

The neurotoxicity of resmethrin was evaluated in three dietary studies on Spraque-Dawley rats designed to examine the gross and histopathological changes to the central and peripheral nervous system. Resmethrin was not neurotoxic when administered at 1,250 mg/kg for 32 weeks, 5,000 mg/kg for 30 days or 12,640 mg/kg for 7 days.

4.8 Metabolism

When the 1-RS *trans* isomer of resmethrin is administered to rats at high concentrations, the alcohol moiety is rapidly absorbed by the gastrointestinal tract. The metabolic transformation occurs primarily by hydrolysis of the ester bond and subsequent oxidation or conjugation of the alcohol and acid moieties. The alcohol moiety was excreted in urine (36%) and feces (64%). The metabolites of the acid moiety included *cis*-hydroxymethyl-chrysanthemic acid and *cis*-chrysanthemum dicarboxylic acid. The principal urinary metabolites from the alcohol moiety are 5-benzyl-3-furancarboxylic acid (BFCA) in free or conjugate form. Several hydroxy derivatives of BFCA are also present in significant quantities. Although there is currently no data on the pharmacokinetics of resmethrin following dermal exposure, in general, dermal absorption of other synthetic pyrethroids is relatively low.

4.9 Cases of human exposure

Although resmethrin has been used for many years, few cases of adverse reactions following exposure to the product have been reported. Resmethrin has been responsible for at least three cases of poisoning in the United States; however, these cases were not well documented and exposure occurred through the use of automatic insecticide dispensers in restaurants.

4.10 Risk assessment

To date, we have been unable to obtain the data required to conduct the same type of risk assessment that was done for malathion. This analysis will be done at a later date, if possible. However, the history of use of resmethrin and the few cases of reported poisoning following intensive and varied use, lead us to believe that the health risks of this product are low.

5. TOXICITY PROFILE OF DICHLORVOS

5.1 Acute toxicity

Dichlorvos is an organophosphate insecticide which has the ability to inhibit RBC ChE, plasma ChE, and brain ChE. It is highly toxic via all routes of exposure (Toxicity Category I or II of the U.S. *Federal Insecticide, Fungicide and Rodenticide Act*).

This insecticide exhibits slight to moderate eye and dermal irritation. In humans, overexposure to dichlorvos causes symptoms which vary depending on the route of exposure. Inhalation of dichlorvos causes respiratory and eye symptoms, while ingestion provokes gastrointestinal effects. Cutaneous absorption can cause perspiration and muscular contractions in the area which has been in contact with the product. In cases of severe exposure, weakness, muscular contractions and fasciculation, paralysis and cardiac irregularities are sometimes found. Paralysis of the respiratory muscles can prove fatal.

The principal acute toxicity indices of dichlorvos are presented in Table 3.

5.2 Subchronic toxicity

Several subchronic studies have been conducted with dichlorvos. Male and female rats have been given oral doses of 0, 0.1, 1.5 and 15 mg/kg/day for 13 weeks. At the dose of 15 mg/kg/day, several rats were observed to salivate abnormally within 30 to 60 minutes of treatment. Urine colouration was also noted at this dose. These effects were observed between the 6th and 12th week in males and between the 8th and 12th week in females. Significant inhibition of plasma ChE activity was observed beginning in the 7th week at doses of 1.5 and 15 mg/kg/day in males and at the dose of 15 mg/kg/day in females. At these same doses, significant reductions in RBC ChE were also noted. After 14 weeks, significant reductions in RBC ChE were observed at the lowest dose. At the highest dose, brain ChE activity was significantly reduced as well. A NOEL of 0.1 mg/kg/day was established for this study, based on the occurrence of RBC ChE inhibition at the dose of 1.5 mg/kg/day.

In another study using rats, which was conducted to evaluate neurobehavioural signs, neuropathological effects and cholinergic activity, animals were tube-fed doses of 0, 0.1, 7.5 and 15 mg/kg/day. When compared with the control group, treated animals showed no significant difference with respect to the battery of functional observation tests, the assessment of locomotor activity, and neuropathological lesions attributable to dichlorvos. At the highest dose and, to a lesser degree, at the intermediate dose, administration of dichlorvos was accompanied by cholinergic signs (e.g., tremors, salivation, lacrimation and exophthalmos). These signs appeared in the 1st week in the rats given the highest dose and in the 3rd week in those given intermediate doses. Plasma ChE inhibition was significant throughout the course of the study. However, RBC ChE inhibition only became significant in the 3rd week in male rats given the highest dose. A NOEL of 0.1 mg/kg/day was determined based on the occurrence of plasma, RBC and brain ChE inhibition, as well as the appearance of cholinergic signs, at the dose of 7.5 mg/kg/day.

In another developmental toxicity study using rabbits showed ChE inhibition at doses similar to those used in the preceding study. A maternal toxicity NOEL of 0.1 mg/kg/day and a Lowest Effect Level (LEL) of 2.5 mg/kg/day were established for this study. When administered via inhalation, the results were similar to those obtain in the oral toxicity study, as well as a NOEL of 0.25 g/L, based on plasma, RBC and brain ChE inhibition. This NOEL value corresponds to a dose of approximately 0.14 mg/kg/day.

A 28-day delayed neurotoxicity study was conducted in which oral doses of 0, 0.3, 1.0 and 3.0 mg/kg/day were administered to hens. The data from this study is suggestive of spinal cord degeneration at doses of 1 and 3.0 mg/kg/day, whereas only minor effects were observed at a dose of 0.3 mg/kg/day. At doses of 1 and 3 mg/kg/day, significant brain ChE inhibition was observed.

5.3 Chronic toxicity and carcinogenicity

Oral and inhalation chronic toxicity studies showed that dichlorvos inhibits plasma, RBC and brain ChE.

In an inhalation chronic toxicity study conducted over a 2-year period with rats, a NOEL value of 0.5 mg/m^3 was established due to these ChE inhibition effects. Assuming 100% absorption and a steady expiratory flow, this concentration roughly corresponds to a dose of 0.055 mg/kg/day.

When male and female dogs were given capsules containing doses of 0, 0.05 (0.1 for the first 3 weeks of the study), 1.0 or 3.0 mg/kg/day for 1 year, various ChE inhibition effects were observed throughout the study. A NOEL value of 0.05 mg/kg/day was established, based on the occurrence of plasma, RBC and brain ChE inhibition.

In a reproductive study of 2 generations of Sprague-Dawley rats given dichlorvos concentrations of 0.5, 20 and 80 ppm in water (males - 0.5, 1.9 and 7.2 mg/kg/day; females - 0.6, 2.3 or 8.3

mg/kg/day), RBC ChE and brain ChE inhibition was observed at every dose level and in both sexes. Significant plasma ChE inhibition effects were also observed in both sexes at the intermediate and high doses. In light of the study results, a NOEL value lower than 5 ppm (males: 0.5 mg/kg/day; females: 0.6 mg/kg/day) was proposed, based on the occurrence of plasma and RBC ChE inhibition.

The Carcinogenicity Peer Review Committee (CPRC) of the U.S. EPA recently concluded that dichlorvos should be classified as a potential human carcinogen (Group C), based on the results of studies conducted in mice and rats. In mice, dichlorvos was found to significantly increase the incidence of stomach cancer.
In rats, dichlorvos was associated with a significant increase in the incidence of leukemia, as well as a non-significant increase in the number of acinar adenomas of the pancreas in males. The classification of dichlorvos is also supported by *in vitro* studies indicating that the product is mutagenic for bacteria, fungi and mammal cells. *In vivo* studies also suggest mutagenic activity. The International Agency for Research on Cancer has classified dichlorvos as a potential human carcinogen (Group 2B).

The chronic toxicity and carcinogenicity profiles of dichlorvos are presented in Table 3.

5.4 Developmental effects

In a reproductive study in mice (5 mg/kg/day) and rats (25 mg/kg/day), survival and growth rates of pups was not affected, although significant ChE inhibition was observed.

Developmental abnormalities were observed in fetuses of rats given intraperitoneal doses of dichlorvos.

In a further study in which Spraque-Dawley rats were given oral doses of 0, 0.1, 3.0 and 21 mg/kg/day between the 6^{th} and 15^{th} day of gestation, significant signs of maternal toxicity were observed at the highest dose. NOEL and LEL values of 3 and 21 mg/kg/day, respectively, were determined for maternal toxicity. Since no toxic developmental effects were observed, the NOEL value for developmental effects is equivalent to or higher than 21 mg/kg/day.

5.5 Reproductive effects

Male and female rats were given 5 mg/kg/day of dichlorvos immediately prior to mating, during pregnancy and while nursing. No reproductive effects were observed, but the dams experienced severe ChE inhibition. Similar results were observed in a study of 3 generations of rats given doses of up to 25 mg/kg/day. The NOEL values for maternal toxicity and reproductive effects are higher than 25 mg/kg/day.

5.6 Mutagenicity

Several studies indicate that dichlorvos is mutagenic for bacteria and mammal cells. However, no mutagenic effects were observed in living animals.

5.7 Neurotoxicity study

The neurotoxic effects of dichlorvos on the central and peripheral nervous systems were evaluated in acute and subchronic studies using rats. In the acute study, rats were given a single dose of 88 mg/kg, while in the subchronic toxicity study, two groups of rats were given a daily dose of 1.6 or 0.8 mg/kg for 6 weeks. The rats in both studies exhibited significant central nervous system changes, increased electroencephalogram (EEG) mean frequencies, reduced EEG amplitude,

reduced central nervous system (CNS) conduction, and increased relative and absolute refractory periods.

An acute neurotoxicity study in rats found a variety of neurological effects (e.g., changes in posture, mobility and gait, tremors) with oral doses of 35 and 70 mg/kg/day. In a delayed neurotoxicity study, hens given a single oral dose of 16.5 mg/kg, followed by a second dose 21 days later, exhibited signs of ChE inhibition shortly after ingesting dichlorvos but signs of delayed toxicity were not observed.

5.8 Metabolism

Dichlorvos is rapidly absorbed by the gastrointestinal tract and promptly broken down primarily by the liver through hydrolysis and, to a lesser degree, dimethylation, without accumulation in the tissues. The main metabolites of *in vivo* hydrolysis are dichloroacetaldehyde and dimethyl phosphoric acid.

5.9 Cases of human exposure

Cases of exposure of humans to dichlorvos have frequently been reported. According to the data base of the U.S. Pesticide Incident Monitoring System (PIMS), 182 incidents of dichlorvos poisoning were reported between 1964 and 1980. Approximately 114 of these cases resulted from the ingestion or dermal exposure to the product and most cases involved children. Similarly, there have been an additional 416 cases of exposure (including 9 deaths) in which dichlorvos has used in combination with other products.

Between 1992 and 1995, the EPA Incident Data System did not report any cases of dichlorvos poisoning in humans.

The California Pesticide Illness Surveillance Program reported 78 cases of exposure to dichlorvos between 1982 and 1990 and these included 60 cases of systemic poisoning, 12 cases of eye irritation and 6 cases of skin irritation.

Finally, the American Association of Poison Control Centers (AAPCC) reported 21,006 cases of exposure involving dichlorvos alone between 1985 and 1992, including 2,671 cases in which the individuals were treated and discharged and 350 cases requiring hospitalization.

5.10 Risk assessment

In 1995, the U.S. EPA conducted an assessment of the risks of exposure to dichlorvos. A number of scenarios were assessed, including risks of exposure for the general population through the food supply and risks for specific categories of workers.

The Agency concluded that risks exceeded benefits for most uses of dichlorvos and recommended a series of measures designed to reduce these risks. The EPA risk assessments indicate that the use of dichlorvos entails carcinogenic risks for the population in food exposure scenarios, as well as significant risks of ChE inhibition for those who mix, load or apply this insecticide and those who return to sites which have been treated.

After having weighed the risks and the benefits, the U.S. EPA moved to cancel the registration of this product for several uses.

Amvac Chemical Corporation has recently informed the U.S. EPA of its intention to voluntarily cancel the registration of dichlorvos for several types of uses, including all aerial applications.

6. TOXICITY PROFILE OF PROPOXUR

Propoxur (2-isopropoxyphenyl methylcarbamate) is most commonly known under the trade name Baygon, although other names are also used. It is commercially available in various forms: wettable powders, granules, powders, emulsifiable concentrates, baits, aerosols, etc. Propoxur is used as a insecticide and a molluscicide. It is one of the active ingredients in several household products (e.g., Raid®). It has also been used extensive to kill mosquitoes as part of malaria control operations. Propoxur does have residual activity and possesses a strong "knock-down" effect.

6.1 Acute toxicity

Propoxur can cause classic signs of ChE inhibition, including: nausea, vomiting, abdominal cramps, diarrhea, excessive salivation and perspiration, fatigue, weakness, rhinorrhea, chest constriction, blurring of vision, lacrimation, loss of coordination, speech impairment, muscular fasciculation, respiratory problems, cyanosis, uncontrolled movements, incontinence, convulsions, coma, or death. Generally speaking, the symptoms induced by propoxur are milder than those associated with organophosphate insecticide poisoning. Propoxur exhibits moderate toxicity via the oral route and low toxicity via the dermal and respiratory routes. It exhibits only slight eye and dermal irritation and is not dermally sensitizing.

There are few experimental studies of human exposure; a small number are briefly reviewed here. A male volunteer (age 42, weight 90 kg) was given a dose of 1.5 mg/kg and experienced a rapid decrease in RBC ChE activity, down to 27% of the normal level. This decrease was rapidly followed by symptoms including blurring of vision, nausea, pallor, perspiration, tachycardia and vomiting. Two hours after the dose was administered, the volunteer had completely recovered. In another study involving a volunteer, a dose of 0.36 mg/kg produced a rapid reduction in RBC ChE activity, down to 57% of the normal level, followed by abdominal discomfort, blurring of vision, moderate facial redness and perspiration. Recovery was complete within three hours. Other volunteers who were given a single dose of 50 or 90 mg appear to have experienced no effects.

The level of toxicity to laboratory-reared animals is relatively constant among species. For example, the oral LD_{50} values are 41 to 104 mg/kg, 23.5 to 109 mg/kg, and 40 mg/kg for rats, mice, and guinea pigs, respectively.

The principal toxicity indices of propoxur are presented in Table 3.

6.2 Subchronic toxicity

In a subchronic toxicity study in which propoxur was administered via the oral route, rabbits were given doses ranging from 50 to 1,000 mg/kg up to a total of 65 treatments (i.e., treatment every 6 hours each day, 5 days per week, over a period of 90 days). Dermal irritation was not observed, nor did the treatments produce other effects with respect to body weight, food intake, hematology, clinical chemical parameters (plasma, RBC and brain ChE), liver enzymes or histopathology.

6.3 Chronic toxicity and carcinogenicity

A committee of the U.S. EPA, the Office of Pesticide Programs Health Effects Division Carcinogenicity Peer Review Committee, has determined that propoxur should be classified in Group B2, as a potential human carcinogen. This classification is based primarily on a carcinogenicity study in mice which demonstrated that propoxur is associated with a significant increase in hepatocellular adenomas in male mice.

In a dietary carcinogenicity study in mice, propoxur was administered in food at doses of 500, 2,000 and 5,000 ppm. A dose-dependent increase in the incidence of hepatocellular adenomas was observed in males. The NOEL value for this study was 500 ppm (114.3 and 150.4 mg/kg/day for males and females respectively). At the intermediate dose, considered to be the LOEL, an increase in liver weight, an increased incidence of liver nodules in males, an increase in aminotransferase activity, an increase in the incidence of ovarian nodules in females, and an increased incidence of bladder hyperplasia were observed.

In a two-year dietary study, doses of 200, 1,000 and 5,000 ppm were administered to rats. At the intermediate dose, a decrease in weight gain was observed in females, as well as an increased incidence of urothelial hyperplasia of the bladder in both sexes. At the highest dose, an increase in the incidence of bladder papillomas and carcinomas was observed. The LOEL for this study was 1,000 ppm (42.03 and 56.16 mg/kg/day for males and females respectively), whereas the NOEL was 200 ppm.

In an inhalation chronic toxicity study, the NOEL was 2.2 mg/m^3 and the LOEL was 10.4 mg/m^3, based on a significant reduction in brain, RBC and plasma ChE activity. As in the preceding study, the presence of bladder papillomas was observed. However, the incidence of these papillomas was low and this research does not appear to have met the criteria formulated by the U.S. EPA.

Finally, in a one-year dietary study, dogs were exposed to propoxur at rates of 200, 600 and 1,800 ppm (values equivalent to 6.77, 22.0 and 98.2 mg/kg/day), with the maximum dose raised to 3,600 ppm in weeks 41 to 44 and 5,400 ppm in subsequent weeks. There does not appear to be a NOEL for this study, since at 200 ppm significant cholesterol elevation was observed; this increase was also noted at the intermediate dose, along with increased n-demethylase activity. At the highest dose, cholinergic signs such as vomiting and increased salivation were observed. RBC ChE activity was reduced at the rate of 1,800 ppm, as was plasma ChE activity in the dogs given the highest dose. In a complementary study lasting 6 months, no effects were noted at the rate of 2.46 mg/kg/day.

6.4 Developmental effects

In a developmental study, rats were given propoxur doses of 0, 3, 9 and 27 mg/kg/day on days 6 to 15 of gestation. Maternal toxicity was observed at the intermediate dose and death was observed at the highest dose rate. However, no indications of fetotoxicity, embryotoxicity or teratogenicity were observed.

In a second, less extensive study, also using rats, pups of females fed 5 mg/kg/day during gestation, exhibited low birth weight, delayed development of some reflexes, as well as evidence of CNS impairment.

A similar study, in which rabbits were given doses of 0, 3, 10 and 30 mg/kg/day, showed maternal toxicity at the highest dose, including death, and a non-significant loss of embryos after implantation.

An additional study using mice showed no evidence of teratogenicity after oral exposure.

6.5 Reproductive effects

The effects of propoxur on reproduction in rats was studied over two generations, by feeding animals of 100, 500 and 2,500 ppm propoxur in their food. The observed NOEL for reproduction was 500 ppm (approximately 45 mg/kg/day) and the LOEL was 2,500 ppm (233 mg/kg/day), based on a reduction in the number of embryo implantation sites. Low birth weight was also observed in pups at this dose level. No NOEL value for parental toxicity was determined, due to the significant decrease in RBC ChE activity at all dose levels.

In a similar study in which the maximum dose was 8 mg/kg/day, a significant decrease in ChE activity was found at the highest dose, though reproductive effects were not observed.

Finally, in a third study, involving three generations of rats, a dose of 18 mg/kg/day was found to cause a reduction in parental food intake, lactation, growth, and litter size. A dose of approximately 2.25 mg/kg/day did not affect fertility, pup growth or litter size, but parental food intake and growth were affected.

6.6 Mutagenicity

The results of various mutagenicity studies suggest that propoxur exhibits little genotoxic activity. In fact, studies conducted to measure mutagenic activity in bacteria and hamster ovary cells, with or without metabolic activity, were, with a few exceptions, negative. Studies on chromosomal aberrations in Chinese hamster ovary cells showed no evidence of clastogens, even though effects were observed at cytotoxic dose levels or with doses exceeding the solubility limit required in order to conduct the tests. In other *in vivo* studies of Chinese hamster bone marrow cells and mouse micronuclei, no genetoxic effects were reported. However, tests for which we do not have an assessment appear to have shown positive results in human lymphocyte cells, as well as in hamster pulmonary cells.

6.7 Neurotoxicity study

In an acute neurotoxicity study involving Wistar rats, propoxur was administered orally, using a feeding tube, at rates of 0, 2, 10 or 25 mg/kg. The neurotoxicity LOEL for this study was established at 2 mg/kg, based on significant inhibition of brain ChE activity. Effects linked to treatment were minimal at this dose. At higher doses, symptoms such as abnormal gait, involuntary clonic movements, respiratory difficulties and diminished activity were observed.

In a 13-week subchronic dietary study, rats were given propoxur at rates equivalent to 0, 33, 132 and 543 mg/kg/day for males, and 0, 39, 163 and 703 mg/kg/day for females. The NOEL for functional observation tests and for changes in motor and locomotor activity was 163 and 543 mg/kg/day for females and males, respectively. The NOEL for ophthalmic changes was 132 mg/kg/day for males and 163 mg/kg/day for females. The effect observed at the highest dose was a reduction in the pupillary reflex, presumably caused by reduced ChE activity. The NOEL for ChE inhibition in females was 39 mg/kg/day and the LOEL was 1,633 mg/kg/day (reduction in brain ChE and plasma ChE at 703 mg/kg/day). In males, the LOEL was 33 mg/kg/day (reduction in brain ChE activity at all test doses and reduction in RBC ChE activity at doses of 132 and 543 mg/kg/day). No microscopic lesions were observed in skeletal and neural muscle tissues.

6.8 Metabolism

Metabolism studies of carbamate insecticides appear to demonstrate that these products are rapidly absorbed via the gastrointestinal and respiratory routes. This is true of propoxur as well. In general, the studies show that propoxur is promptly absorbed after ingestion and rapidly metabolized. It is excreted primarily in the urine. One of the main metabolites observed in urine, 2-isopropoxyphenol, can be used for the purposes of biological follow-up of occupational

exposure in workers. There is a correlation between total excretion of propoxur and total dermal exposure.

In dermal absorption studies where 6 volunteers were given a single dermal dose equivalent to 4 g/cm^2 for a total exposure time of 24 hours, the quantity excreted in urine corresponded to 19.6% of the quantity administered dermally. By comparison, a dose administered intravenously was excreted at a rate of 81.8%. Studies in rats have demonstrated that a non-linear decrease of dermal absorption with increase of dosage. In some case, the level of absorption can reach 50%. However, since the product was administered in a solvent to facilitate penetration, it is felt that studies in humans are more appropriate for predicting effects under field conditions.

6.9 Cases of human exposure

According to the OPP's Incident Data System there were 91 cases of human exposure to propoxur in the United States between 1992 and April 1996. The majority of these cases (70) were linked to two specific incidents involving post-application exposures. The symptoms experienced included headaches, nausea, depression and respiratory irritation.

The California Pesticide Illness Surveillance Program reported 125 cases in which persons exhibited systemic symptoms following exposure to propoxur. Close to half of the persons affected experienced respiratory problems including coughing, chest constriction, shortness of breath and congestion.

6.10 Risk assessment

No data were found concerning assessments of the risks associated with the use of propoxur to control mosquitoes. The U.S. EPA has assessed the risks associated with other uses of this product, such as the treatment of cracks and crevasses, aerosol applications, tick and lice collars, and localized treatments.

According to these assessments, the carcinogenic risk linked to food consumption, based on the tolerance levels proposed in the United States, is 3.4 cases X 10^{-7} person for the general population. The risks associated with drinking water are negligible under the conditions studied.

With respect to the types of uses listed in the introduction to this section, the EPA concludes that the aggregate risks for the general population, as well as for children considered as a sub-group, are negligible.

However, we cannot discount the risks of significant exposure in the context of ground- or aerial-based application to control mosquitoes. Unfortunately, we do not have sufficient data at this time to conduct an assessment of potential risks.

7. CONSIDERATIONS IN SELECTING AN ADULTICIDE

The large-scale use of adulticides is more problematic than larvicides uses because it entails the possibility of higher levels of exposure, particularly with aerial application. Needless to say, the selection of an insecticide will have to be made based on the degree of safety it offers.

The currently registered adulticides do not appear to exhibit comparable acute toxicities. Permethrin may only be used as a barrier treatment and, because it exhibits a low acute toxicity, it should pose limited risks to the health of residents or insecticide applicators provided measures are taken to avoid significant levels

of exposure. The measures (e.g., workers training, personnel protective equipment, respect of a buffer zone, public information) proposed by GDG Environnment should ensure the safety of the groups concerned.

In our view, dichlorvos exhibits a level of toxicity which is too high for it to be utilized to control mosquitoes. In addition to being a powerful ChE inhibitor, dichlorvos has a carcinogenic potential which is far from negligible. In addition, the numerous cases of poisoning in humans reported in the literature also argue against its use.

Although carbamate insecticides are generally less toxic than organophosphates, propoxur is nonetheless a ChE inhibitor of moderate toxicity and is probably carcinogenic. Based on these factors, we feel that it should not be used unless no other alternatives are available.

Although malathion appear to offer an acceptable safety level, there are several factors which make it use less tenable than other adulticides. Throughout its history of use in the United States there have been numerous cases of poisoning with this product. Given that it will be difficult to control additional residential uses if we were faced with a situation requiring the control of adult insects, we would have to consider the possibility of cases of poisoning in the public. The risk assessment of malathion conducted by the U.S. EPA reveals risks of dermal and inhalation exposure for several residential use scenarios. What, then, will be the impact of this type of use, in combination with treatments, applied by professional mosquito abatement companies? Moreover, it is possible that the public will use other organophosphates. Since all organophosphates share the same mechanism of toxicity and, in addition, ChE inhibition effects can be cumulative, the risks could be significantly increased.

The second consideration that leads us to opt for resmethrin is the uncertainty that persists regarding the carcinogenic potential of malathion. Although tumorigenic effects were observed at very high doses only, the Cancer Assessment Review Committee classified malathion as exhibiting suggestive evidence of carcinogenicity.

Malaoxon, a decomposition product in water, is much more toxic than malathion. In the event of an accidental spill in a source of drinking water, the risks of poisoning could be very high if immediate measures are not taken to prohibit consumption.

Given the fact that it possesses a high soil mobility potential, malathion is capable of contaminating groundwater sources. Moreover, its half-life in water is greater than that of all the products we studied. Malathion is less toxic to fish than resmethrin, but laboratory data indicates that it can be highly toxic to aquatic invertebrates, as well as to amphibians during the aquatic stage of their lives. Like all of the products assessed, malathion is highly toxic to bees.

Apart from the toxicological considerations, malathion has a number of drawbacks associated with its physicochemical properties. It can be corrosive to metals and also attacks some plastics, rubbers and other finishes. It also has a relatively strong odour which, according to U.S. data, can easily make hypersensitive individuals ill. The odour associated with malathion can also make its use less acceptable to the public. The general public often equate strong odours with high levels of toxicity. Thus in an areas where WNV activity is detected, it may be difficult to convince individuals that multiple applications of adulticide (which they perceive to be highly toxic) are needed to control mosquitoes.

Although resmethrin has fewer drawbacks than malathion, we cannot overlook the fact that it does exhibit potential toxicity. As with all pesticides, safety procedures will have to be met when using the product. In addition, resmethrin can bioaccumulate in certain aquatic organisms (e.g., some species of fish do not readily metabolize pyrethroids and these products are a highly toxic to these organisms). The use of this product will therefore require that all technical measures are taken to avoid contamination of rivers and streams.

Resmethrin, although not highly toxic to mammals, has a better "knock-down" effect on mosquitoes than the organophosphates and is generally very effective at low doses. The fact that there are water-based formulations is another clear advantage.

Malathion is currently registered in Canada for both ground- and aerial based Ultra-low volume (ULV) applications whereas, resmethrin is only registered for ground use. However, formulations containing resmethrin (e.g., Scourge) are registered in the United States for aerial application. When selecting an adulticide to control the incidence of mosquito-borne diseases, the fact that a product is not registered should not outweigh its toxicological characteristics.

Table 5 presents a comparison of the main factors which guided our selection of an insecticide.

8. RECOMMENDATIONS

•Whenever possible, resmethrin should be considered the adulticide of choice for the control of mosquitoes potentially infected with WNV.

•Immediate steps should be taken to obtain emergency registration for resmethrin for the control of mosquitoes using aerial-based ULV equipment.

•Regardless of which product is selected, effective preventive measures will have to be taken to ensure safe and effective use of the adulticides with a minimal impact on the environment (e.g., communications plan, protection measures for the public and insecticide applicators, programs to monitor for potential health effects in the general public and applicators, non-target effects, etc.).

Table 2. Summary of the physicochemical properties and environmental characteristics of dichlorvos, malathion, permethrin, propoxur, and resmethrin

Parameters	Dichlorvos	Malathion	Permethrin	Propoxur	Resmethrin
CAS Registry No.	62-73-7	121-75-5	52645-53-1	114-26-1	10453-86-8*
Grade	technical	technical	technical	technical	technical
Physical state	liquid	liquid	solid	solid	solid
Vapour pressure (mm Hg)	1.57×10^{-2} at 25ºC	4×10^{-5} at 30ºC	3.4×10^{-7} at 25ºC	3×10^{-6} at 20ºC	1.1×10^{-8} at 30ºC
Water solubility (mg/L)	16,000 at 25ºC	145 at 25ºC	0.2 at 30ºC	1,860 at 20ºC	insoluble at 25ºC
Mobility in soil	high	high	not highly mobile	high	probably not highly mobile
Half-life in soil	7 days	< 1 day	< 28 days	14 to 120 days	30 days
Half-life in water	20 to 80 hours	173 days	< 2.5 days	1 to 7 days	47 minutes to 36.5 days
Groundwater contamination potential	moderate	low to moderate	low	low	low
Bio accumulation potential	low	low	high in fish	low	possible in fish

* This product is comprised of the two isomers: cis-resmethrin (30%) and trans-resmethrin (70%)

Table 3. Summary of the toxicity indicators for dichlorvos, malathion, permethrin, propoxur, and resmethrin

Parameters	Dichlorvos	Malathion	Permethrin	Propoxur	Resmethrin
Chemical class	Organophosphate	Organophosphate	Synthetic pyrethroid	Carbamate	Synthetic pyrethroid
Principal mechanism of toxicity	cholinesterase (ChE) inhibition	ChE inhibition	alteration of the ionic permeability of the axonal membrane affecting propagation of nerve impulses	ChE inhibition	alteration of the ionic permeability of the axonal membrane affecting propagation of nerve impulses
Metabolites and/or degradation products	dichloroacetaldehyde and dimethyl phosphoric acid	malaoxon (more toxic than the parent compound)	several, including Cl_2CA	2-isopropoxyphenol	several, including BFCA
Acute oral toxicity in rats (mg/kg)	LD_{50} 17 to 80	LD_{50} 2,100 to 5,700	LD_{50} 500 to > 4,000[a]	LD_{50} 41 to 104	LD_{50} 1,244 to 4,250[a]
Acute dermal toxicity in rats (mg/kg)	LD_{50} 70 to 250	LD_{50} > 2,000	LD_{50} > 4,000	LD_{50} > 2,000 rabbits	LD_{50} 2,500
Acute inhalation toxicity in rats (mg/m^3)	LC_{50} 340 rats (4 hours)	LC_{50} > 5.2 (4 hours)	LC_{50} > 685 (3 hours) to > 12,000 (1 hour)	LC_{50} > 500 (4 hours) 1,440 (1 hour)	> 9,500 (4 hours)
Toxicity class based on U.S. EPA classification	I	III	III	II	III
Dermal irritation class based on U.S. EPA classification	IV	IV	IV	IV	IV
Eye irritation class based on U.S. EPA classification	III	III	IV	III	IV
Sensitization Inhalation toxicity in subchronic toxicity studies with rats	no NOEL[b] (rabbit) 250 ug/m^3 based on plasma and RBC ChE inhibition	no LOAEL[c] (systemic) 100 mg/m^3 based on histopathological lesions of the nasal cavity and larynx LOAEL (ChE) 100 mg/m^3 Inhibition of plasma and RBC ChE in females	no at 500 mg/m^3 , tremors and convulsions appeared in the first week but disappeared in the second week	no rat: 2-year chronic toxicity study NOEL 2.2 mg/m^3 LOEL 10.4 mg/m^3 (decrease in ChE activity)	no NOEL 100 mg/m^3, LOEL 300 mg/m^3 with minor effects on several chemical parameters and signs of irritation LOEL 100 mg/m^3, changes in behaviour, blood chemistry and decreased body weight in females.

Oncogenicity	rat: increase in cases of leukemia and a non-significant increase in the number of acinar adenomas of the pancreas mouse: increased incidence of stomach cancer	rat: increased incidence of liver tumours (female) at excessive doses only. mouse: increased incidence of liver tumours at excessive doses only. malaoxon: negative in mice	rat: negative mice: could induce pulmonary tumours	mouse: significant increase in the incidence of hepatocellular adenomas in males	rats and mice: negative
Mutagenicity	mutagenic for bacteria and mammal cells	According to the U.S. EPA, malathion does not cause chromosome damage, gene mutations or unscheduled DNA synthesis	Studies available in the literature all gave negative results.	most of the available studies showed negative results	Studies available in the literature all gave negative results.

Chronic oral toxicity	dog: NOEL 0.05 mg/kg/day (decrease in plasma, RBC and brain ChE activity) rat: NOEL 0.5/0.6 mg/kg/day (males/females) (plasma ChE and RBC ChE inhibition)	rat: NOAEL[d] 2.4 mg/kg/day LOAEL 29 mg/kg/day (inhibition of plasma ChE activity) mouse: systemic NOAEL 143/167 mg/kg/day (male/female) and LOAEL 1476/1707 mg/kg/day (decrease in body weight and food intake, increase in liver weight and hypertrophy of hepatocytes. NOAEL (ChE) 17.4/20.8 mg/kg/day, LOAEL 143/167 mg/kg/day (inhibition of plasma and RBC ChE in both sexes) Malaoxon: rat systemic NOAEL: 1 mg/kg/day LOAEL 57/68 mg/kg/day (increased mortality and microscopic changes in the tissue of the nasal cavity and tympanic cavity in females, increase in incidence on mineral deposits in the stomach in males) LOAEL ChE 1 mg/kg/day (inhibition of plasma ChE after 6 months of treatment)	rat: NOEL 5 mg/kg/day LOEL 25 mg/kg/day (increase in liver weight) dog: NOEL 5 mg/kg/day LOEL 100 mg/kg/day (increase in alkaline phosphatase activity and liver weight and hepatocellular swelling	mouse: NOEL 500 ppm (114.3 and 150.4 mg/kg/day for males and females) LOEL 2,000 ppm (increased: liver weight, incidence of liver nodules in males, aminotransferase activity, incidence of ovarian nodules, and hyperplasia of the bladder) rat: NOEL 200 ppm (42.03 and 56.16 mg/kg/day in males and females) LOEL 1,000 ppm (decreased weight gain, increased incidence of urothelial hyperplasia of the bladder) dog: NOEL - none LOEL - 200 ppm (6.77 mg/kg/day) elevated cholesterol levels and increased n-demethylase activity	rat: no NOEL, LOEL 40 mg/kg/day (lowest dose tested, hypertrophy of the liver and decrease in body weight in rats) dog: NOEL 10 mg/kg/day LOEL 30 mg/kg/day (increase in liver weight)
Oral reproductive toxicity studies	rat: parental: NOEL for maternal toxicity - 5 mg/kg/day NOEL for reproductive effects - 25 mg/kg/day	rat: parental: NOEL 394/451 mg/kg/day (male/female), LOEL 611/703 mg/kg/day (decrease in body weight) pups: NOEL 153 mg/kg/day, LOEL 451 mg/kg/day (decrease in weight gain during lactation	rat: no NOEL LOEL 25 mg/kg/day (hypertrophy of centrilobular hepatocytes)	rat: NOEL 45 mg/kg/day LOEL 233 mg/kg/day (reduction in the number of embryo implantation sites) rat: no NOEL (2.25 mg/kg/day: food intake and parental growth pups: LOEL 18 mg/kg/day (reduced lactation, growth and litter size).	rat: no NOEL, LOEL 25 mg/kg/day (increase in number of pups cast dead and reduced body weight of pups during weaning)

Oral developmental toxicity study	rat: NOEL for maternal toxicity - 3 mg/kg/day LOEL for maternal toxicity: 21 mg/kg/day NOEL for developmental effects 21 mg/kg/day	rat: NOEL 400 mg/kg/day, LOEL 800 mg/kg/day for maternal effects (decrease in weight gain and food intake) NOEL 800 mg/kg/day for developmental effects (highest dose tested) mouse: NOEL 150 mg/kg/day (highest dose tested) rabbit: NOEL 25 mg/kg/day, LOEL 50 mg/kg/day for maternal effects (decrease in weight gain) and for developmental effects (increase in average percentage of non-implanted fertilized eggs)	rat: NOEL 200 mg/kg/day for maternal effects and developmental effects (highest dose tested) rabbit: NOEL 400 mg/kg/day for maternal effects and developmental effects (highest dose tested)	rat: NOEL 3 mg/kg/day LOEL 9 mg/kg/day (maternal toxicity but no fetotoxicity, embryotoxicity or teratogenicity) rat: pups LOEL 5 mg/kg/day (low birth weight, delayed development of some reflexes, CNS impairment).	rat: NOEL 40 mg/kg/day, LOEL 80 mg/kg/day for maternal effects (decrease in body weight) and for developmental effects (delayed skeletal development) ; NOEL 80 mg/kg/day for teratogenic effects (highest dose tested) rabbit: NOEL 100 mg/kg/day for maternal effects and developmental effects (highest dose tested)

[a] The values for synthetic pyrethroids are highly variable due to isomer ratios, the vehicle used for oral administration and the species of test animal
[b] NOEL: No observed effect level; [C] LOAEL: Lowest observed adverse effect level; [d] NOAEL: No observed adverse effect level

Table 4. Reference values (reference doses) for the assessment of human exposure for dichlorvos, malathion, permethrin, propoxur, and resmethrin

Parameters	**Dichlorvos[a]**	**Malathion[a]**	**Permethrin[a]**	**Propoxur[b]**	**Resmethrin[a]**
Critical effects	RBC ChE and plasma ChE inhibition in dogs	inhibition of plasma and RBC ChE activity in humans	increase in liver weight	humans: mild cholinergic symptoms and RBC ChE inhibition	reproductive toxicity in rats
NOEL	NOAEL 0.05 mg/kg/day	0.2 mg/kg/day	5 mg/kg/day	none	none
LOEL	LOAEL 0.1 mg/kg/day	0.3 mg/kg/day	25 mg/kg/day	LEL 0.15 mg/kg/day	LEL 25 mg/kg/day
Factor of uncertainty on the NOEL value[a]	100 on the NOEL	10	100	30 on the LEL	1,000 on the LEL
Reference oral dose	0.0005 mg/kg/day	0.02 mg/kg/day	0.005 mg/kg/day	0.005 mg/kg/day	0.03 mg/kg/day
Level of confidence in the reference dose level[a]	moderate	moderate	high	moderate	high

Drinking water quality guidelines (ug/L)	not available	190[c]	20d[b]	not available	not available

[a] IRIS : Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, D.C. (Delivery method CD-ROM), MICROMEDEX, Englewood, Colorado (Edition expires December 31, 2000).

[b] U.S. EPA : United States Environmental Protection Agency, 1997. Reregistration Eligibility Decision (RED), PROPOXUR. Prevention, Pesticides and Toxic Substances (7508W), EPA738-R-97-009, August 1997.

[c] Health Canada, 1996. *Guidelines for Canadian Drinking Water Quality, 1996, Supporting Documents*, Prepared by the Federal-Provincial Subcommittee on Drinking Water, Health Canada, Health Protection Branch, Ottawa.

[d] WHO, 1994. *Drinking Water Guidelines, Volume 1 : Recommendations*, 2nd Edition, Geneva, 202 pages.

Table 5. Comparison indices for adulticides

Parameters	**Dichlorvos**	**Malathion**	**permethrin**	**Propoxur**	**Resmethrin**
Cholinesterase inhibition	yes	yes	no	yes	no
FIFRA acute toxicity classification	I	III	III	II	III
Documented cases of acute poisoning	significant number	significant number	very few	moderate number	very few
Carcinogenic potential	possibility	suggestive evidence	no	probable	no
Reproductive and developmental effects	no	no	slight possibility of embryotoxic effects	delayed developmental of some reflexes and CNS impairment in rats	in rats, slight increase in the number of still-born pups
Groundwater contamination potential	moderate	low to moderate	low	low	low
Half-life in water	20 - 80 days	173 days	< 2.5 days	1 - 7 days	47 minutes to 36.5 days

Bio-accumulation potential	low	low	high in fish	low	possible in fish
Toxicity in fish (LC_{50} rainbow trout ug/L)	100	2.8	0.62	3,700	0.275
Toxicity in bees (oral LD_{50} ug/bee)	0.29	0.38	0.098	highly toxic (value not specified)	0.069

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