AVERMECTINS: POTENTIAL ENVIRONMENTAL RISKS AND IMPACTS ON FRESHWATER ECOSYSTEMS IN QUEBEC

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Avermectins: Potential Environmental Risks and Impacts on Freshwater Ecosystems in Quebec

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Management Perspective

Advances in biotechnology and the intensification of agriculture have led to major increases in the use of pharmaceutical products and other chemicals to maintain animal and human health. Freshwater ecosystems in the Montreal region and surrounding areas are subject to point and non-point sources of agricultural and industrial pollution. Surprisingly little is known about the dangers these compounds pose to freshwater ecosystems. One of the most commonly used veterinary drugs is a family of anti-parasitic compounds called avermectins. Avermectins control parasitic infections in humans, domestic pets, livestock and farmed fish. The objective of this report is to thoroughly review the known environmental impacts of avermectins and to assess the risk associated with their use in Quebec to freshwater ecosystems. Publication was made possible by the St. Lawrence Vision 2000 Action Plan, a Canada–Quebec initiative aimed at understanding, protecting and restoring the St. Lawrence ecosystem.

Perspective de gestion

Les progrès de la biotechnologie et l'intensification de l'agriculture ont conduit à une utilisation accrue de produits pharmaceutiques et autres produits chimiques pour protéger la santé humaine et animale. Les écosystèmes d'eau douce de la région de Montréal et de zones avoisinantes sont soumis à une pollution ponctuelle et diffuse par l'industrie et l'agriculture. De façon surprenante, on connaît peu les dangers que certains produits comme les avermectines présentent pour les écosystèmes d'eau douce. Les avermectines, des produits pharmaceutiques parmi les plus utilisés en médecine vétérinaire, sont une famille de composés antiparasitaires. Les avermectines contrôlent les infections parasitaires chez les humains, les animaux domestiques, le bétail et les poissons d'aquaculture. Le présent rapport vise à faire une revue approfondie des impacts connus des avermectines sur l'environnement et à évaluer le risque que leur utilisation au Québec présente pour les écosystèmes d'eau douce. Ce document a été produit dans le cadre du Plan d'action fédéral-provincial Saint-Laurent Vision 2000 qui vise à comprendre, protéger et restaurer l'écosystème du Saint-Laurent.

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Abstract

Avermectins are a class of anti-parasitic (anthelmintic) compounds widely used to treat ecto- and endoparasites of humans, livestock and domestic pets, as well as ectoparasites of fish in the aquaculture industry. Their potency and effectiveness against a wide range of common pests have made avermectins one of the world's most popular anthelmintics. The physical and chemical properties of avermectins include low solubility in water, high affinity for binding to organic particles and soil half-lives of 93 to 217 days. A large proportion (80–98%) of administered doses can be excreted via the feces of treated animals. Avermectins can accumulate and persist in dung for extended periods of time (up to two months) and can exert lethal and sublethal effects on a range of non-target invertebrates, such as dipterans, coleopterans and benthic invertebrates. Because they are generally released into the environment through the manure of treated animals, the total amount of avermectins entering the environment will be mitigated by the number and type of livestock in a region, manure management practices and other farming practices. In Quebec, livestock numbers are dominated by pigs, followed by dairy and beef cattle. However, cattle contribute a greater proportion to the total manure production owing to their larger body sizes. Avermectins can enter freshwater systems from agriculture by one or a combination of four routes: 1) runoff; 2) groundwater seepage; 3) direct deposition; and 4) soil erosion. Smaller amounts may enter via sewage from urban sources. The physical/chemical properties of avermectins prevent runoff and groundwater seepage from acting as major sources of contamination. Rates of soil erosion in Quebec range from 1 to 11 tonnes per hectare in some watersheds. At this rate, 200 to 2200 mg of ivermectin, a form of avermectin, can be transported into adjacent waterbodies. The direct deposition of avermectins poses the greatest threat to freshwater ecosystems and can potentially result in concentrations of 0.042 to 0.38 ppm in ponds adjacent to agricultural areas. The estimated total amount of ivermectin given to livestock in Quebec ranges from 206 to 378 kg per year, depending on assumptions made about treatment regimes.

Résumé

Les avermectines sont une classe de substances antiparasitaires (anthelminthiques) utilisées à grande échelle pour combattre les ectoparasites et les endoparasites chez les humains, le bétail, les animaux domestiques, ainsi que les ectoparasites chez les poissons d'aquaculture. La puissance et l'efficacité des avermectines pour lutter contre une grande variété de parasites les ont propulsées au premier rang des anthelminthiques. Les propriétés physiques et chimiques des avermectines incluent une faible solubilité dans l'eau, une grande affinité pour se lier aux particules organiques et une demi-vie dans le sol de 93 à 217 jours. De 80 % à 98 % des doses administrées peuvent être expulsées dans les déjections des animaux traités. Les avermectines peuvent s'accumuler et persister dans les déjections animales pendant de longues périodes (jusqu'à deux mois) et avoir des effets létaux et sublétaux sur un éventail d'invertébrés non visés, comme les Diptères, les Coléoptères et des organismes benthiques. Parce que leur pénétration dans l'environnement se fait par l'intermédiaire des déjections d'animaux traités, la quantité totale d'avermectines dépend du nombre de têtes de bétail dans une région, du type de bétail, des pratiques de gestion des fumiers et des autres pratiques agricoles. Au Québec, les élevages de porcs sont les plus nombreux, suivis par les élevages laitiers et les élevages de bovins. Toutefois, les élevages de bovins contribuent la plus grande proportion de fumier à cause de la taille des animaux. Les avermectines peuvent pénétrer dans les écosystèmes d'eau douce par quatre voies : 1) par ruissellement; 2) par infiltration de la nappe phréatique; 3) par dépôt direct; et 4) par l'érosion des sols. De plus petites quantités peuvent pénétrer par les eaux usées urbaines. Les propriétés physiques et chimiques des avermectines empêchent les eaux de ruissellement et d'infiltration des eaux souterraines d'agir comme source majeure de contamination. Au Québec, la vitesse d'érosion atteint de 1 à 11 tonnes par hectare dans certains bassins versants. À ce taux, 200 à 2200 mg d'ivermectine pourraient être transportés vers des plans d'eau adjacents. Le dépôt direct d'avermectines pose le plus grand danger pour les écosystèmes d'eau douce et pourrait résulter en concentrations de 0,042 à 0,38 ppm dans les étangs voisins de zones agricoles. La quantité totale d'ivermectine administrée au bétail au Québec s'élève à 206 à 378 kg par année, selon les hypothèses avancées au sujet des régimes de traitement.

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Definitions

Animal unit: A measurement based on the number of animals it takes to produce the 73 kilograms of nitrogen required to fertilize one acre of corn for one year. The number of animals of a given kind in one animal unit is expressed as a coefficient. One cow, for example, equals approximately one animal unit, whereas four sows are equivalent to one animal unit.

Bioconcentration factor (BCF): A measure of the tendency for a substance in water to accumulate in fish tissue or in tissues of other organisms.

Fluctuating asymmetry: Widely used to measure developmental stability. The developmental stability of an organism is reflected in its ability to produce an "ideal" form under a particular set of conditions. The lower its stability, the greater the likelihood it will depart from this ideal form. Ideal forms are rarely known *a priori*. However, bilateral structures in bilaterally symmetrical organisms offer a precise ideal, perfect symmetry, against which departures may be compared. These structures either show no change or these changes increase with increasing extrinsic (environmental) or intrinsic (predominantly genetic) "stress."

Adsorption coefficient (K_{oc}): A measure of the tendency for organic substances to be adsorbed by soil and sediment, expressed as: K_{OC} = (mg substance adsorbed/kg organic carbon)/(mg substance dissolved/litre of solution). The K_{OC} is substance-specific and largely independent of soil properties.

Octanol/water partitioning coefficient (K_{ow}): A measure of the equilibrium distribution of an organic contaminant dissolved in water between the aqueous phase and an immiscible organic phase. K_{ow} = (concentration in octanol phase)/(concentration in aqueous phase). A compound with a high K_{ow} is considered relatively hydrophobic and would tend to have low water solubility, a large soil/sediment adsorption coefficient, and a large bioconcentration factor.

LC_{50}: Concentration of a potentially toxic substance in an environmental medium that causes death to 50% of a test population following a certain period of exposure.

List of Abbreviations

BAPE	Bureau d'Audiences Publiques sur l'Environnement
BCF	Bioconcentration Factor
CBE	Conseil de Bassin de la rivière Etchemin
FDAH	Fort Dodge Animal Health (Wyeth Inc.)
GABA	Gamma-Aminobutyric Acid
GluCl	Glutamate-gated Chloride Channels
HPLC	High Performance Liquid Chromatography
IGF-I	Insulin-like Growth Factor-I
ISQ	Institut de la Statistique du Québec
LH	Luteinizing Hormone
MAPAQ	Ministère de l'Agriculture, des Pêcheries, et de l'Alimentation
MENVQ	Ministère de l'Environnement du Québec
MIH	Moult-Inhibiting Hormone
PEC	Predicted Environmental Concentration
RIFA	Red Imported Fire Ant
SLC	St. Lawrence Centre
UMFV	Université de Montréal, Faculté de Médecine Vétérinaire

1 Introduction

Pharmaceutical products originating from municipal, industrial and agricultural wastes have been detected in freshwater ecosystems downstream of areas of heavy urbanization and intensive livestock production (Orlando et al. 2004, Kolpin et al. 2002). Advances in biotechnology and the intensification of agriculture have led to major increases in the use of fertilizers, pesticides and medicines to maintain animal and human health, and sustain high levels of livestock production. Despite the agriculture sector's heavy reliance on veterinary pharmaceutical drugs, very little is known about the dangers they pose to freshwater ecosystems. In fact, the Quebec Order of Veterinarians has stated that no research has been conducted in Quebec on the environmental risks of drug residuals originating from livestock (BAPE 2003). Recent work that directly links the environmental fate of veterinary medicines with precipitous declines in wild vulture populations (Oaks et al. 2004) highlights the potentially hazardous and generally unknown fate of these drugs.

Parasite infections, even at sub-clinical levels, can decrease the growth, maturity and productivity of livestock (DesCôteaux et al. 2001). Gastrointestinal nematode infections are considered to be one of the most important production-limiting diseases of ruminant livestock (Sanchez et al. 2002). There are therefore strong financial incentives for farmers to include parasite control in their herd management practices, including using anthelmintic medications. One class of pharmaceuticals that has been a boon to the livestock industry is avermectins, also known as macrocyclic lactones.

Avermectins were discovered in 1981 when a group of researchers isolated the compound from the soil bacterium *Streptomyces avermitilis*. Since that time, several different forms of avermectins have been developed, and they have become the most widely used groups of drugs for treating parasitic infections. Avermectins have been approved for use in humans, domestic pets, cattle, sheep, swine, horses, camels, bison, deer, goats, foxes and reindeer. Since their introduction to the market, over 5 billion doses of avermectin products have been sold worldwide (Shoop and Soll 2002), making them the world's most widely used antiparasitic drug.

Many researchers have raised concerns about the potential for avermectins to exert negative impacts on non-target fauna. The environmental impacts of avermectins have been

extensively studied in terrestrial ecosystems and to a lesser degree in coastal marine ecosystems. To date, little work has been done on their potential impacts on freshwater ecosystems. Although the physical/chemical data on avermectins suggest that they are unlikely to accumulate in the water column of freshwater systems (Halley et al. 1989a), these parameters also indicate that they may pose a significant threat to benthic freshwater organisms.

1.1 GENERAL PROPERTIES

Avermectins are a group of compounds produced from the fermentation broth of the bacterium *Streptomyces avermitilis*. All avermectins possess a rigid 16-membered lactone ring system. Within the family of the avermectins, there exist two series, A and B, within which are two structural subsets, designated 1 and 2, consisting of two homologs, a and b. These components combine to form eight different varieties of avermectins: A1a, A2a, B1a and B2a, and A1b, A2b, B1b and B2b. The various designations reflect minor differences in the chemical structure of the lactone ring[1]. The a and b components have virtually identical activities and are generally not fully separated in the fermentation broth. This has resulted in a simplification of the nomenclature of the structures to A1, B1, A2, and B2 (Shoop and Soll 2002). When the mixture of homologs in the fermentation broth contains 80% or more of the 'a' and 20% or less of the 'b' compound, it is referred to as avermectin. Ivermectin (22, 23-dihydroavermectin B1) is a semi-synthetic hybrid of avermectin-B1 and B2 (Shoop and Soll 2002). It was the first avermectin to be produced commercially and is generally used to control the ecto- and endoparasites (mites and nematodes) of livestock, humans and domestic pets. Other forms of avermectin are also available commercially (Table 1). Avermectin-B1, commonly referred to as abamectin, is used as a pesticide in the horticulture industry to control mites and other crop pests. However, ivermectin remains the most common form and as a result, it is the form for which there is the most toxicological information, particularly with respect to its use in cattle.

A search in Health Canada's drug product database found 23 products that contain ivermectin as an active ingredient. Most of these are registered trademarks of Merial, a veterinary

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[1] The A compounds possess a methoxyl group at C-5, the B-group compounds have a hydroxyl function at C-5; the 1-components have a double bond between C-22 and C-23, the 2-components have a single bond with a hydroxyl group at C-23; the a-components have a secondary butyl group at C-25, the b-components have an isopropyl moiety at C-25.

pharmaceutical company jointly owned by Merck and Co., Inc. and Aventis S.A. (Table 1). The existing patents for avermectin products are ending and therefore more generics may soon be introduced into the market. As a result, the total use of avermectins may increase, as prices generally drop when generics are introduced. However, some industry representatives feel that new formulations would only change the market share of any given product and not necessarily increase the total amount used (McKellar 1997).

Table 1
Pharmaceutical products containing avermectin registered for use in Canada

Brand name	Formulation	Dosage	Target animal	Manufacturer
Noromectin	Injection	0.2 mg/kg	Cattle and swine	Norbrook
Ivomec	Injection	0.2 mg/kg	Cattle, sheep, swine	Merial
Ivomec	Pour-on	0.5 mg/kg	Cattle	Merial
Panomec	Oral	0.2 mg/kg	Horses	Merial
Ivomec	Premix food	2 mg/ kg food	Swine	Merial
Eqvalan	Oral	0.2 mg/kg	Horses	Merial
Zimecterin	Oral	0.2 mg/kg	Horses	Merial
Ivomec drench	Oral		Sheep	Merial
Ivomec	Bolus*	12 mg/kg/day	Cattle	Merial
Eqvalan	Oral	0.2 mg/kg	Horses	Merial
Eprinex	Pour-on	0.5 mg/kg	Beef and dairy cattle	Merial
Dectomax	Pour-on	0.5 mg/kg	Cattle and swine	Pfizer
Dectomax	Injection	0.2 mg/kg	Cattle and swine	Pfizer
Cydectin	Injection	0.5 mg/kg	Cattle	Wyeth
Cydectin	Pour-on	0.5 mg/kg	Beef and dairy cattle	Wyeth
Quest gel	Oral	0.4 mg/kg	Horses	Wyeth

Source: Health Canada, 2004. <http://www.hc-sc.gc.ca/hpb/drugs-dpd/index.html>.

* The sustainable-release bolus is no longer available in Canada.

1.2 PHYSICAL/CHEMICAL PROPERTIES

The physical/chemical properties of a compound largely determine its fate in the environment. The high vapour pressure of avermectins indicates that they are unlikely to

volatilize and be distributed into the atmosphere (Bloom and Matheson 1993). The solubility of avermectins in water is relatively low. However, they are soluble in methanol, chloroform, p-dioxane, dimethylformamide, ethyl acetate, 95% ethanol, diethyl ether, methylene chloride, acetone and aromatic hydrocarbons. Avermectins also have a high adsorption coefficient (K_{oc}), indicating that they are not likely to accumulate in the water column but will readily bind tightly to organic carbon. This was confirmed by tests that measured the degree of binding between ivermectin and a wide variety of soil types (Halley et al. 1989a). The octanol/water coefficient (K_{ow}) is an indication of a compound's affinity for lipids. The K_{ow} of ivermectin is high enough to raise concerns about it bioconcentrating in fat tissues of aquatic species. The high K_{ow} of ivermectin is likely balanced by its large molecular weight, making it difficult to cross biological membranes.

Ivermectin has been shown to undergo rapid photodegradation as a thin, dry film on glass with an estimated half-life of 3 h (Halley et al. 1989a). Near the surface of open water under clear skies, the half-life of ivermectin is 12 h in summer and 39 h in winter (Halley et al. 1989a). The degradation half-lives of ivermectin in soil/feces mixtures have been determined under laboratory conditions and in outdoor conditions for winter and summer (Table 2). These results indicate that ivermectin can remain in the environment, bound to soil, for a considerable period of time.

Concentrations of avermectins are generally measured using high-performance liquid chromatography (HPLC). Measurement occurs in three phases: 1) extraction of ivermectin from samples and subsequent purification; 2) derivatization into corresponding fluorophores; and 3) quantification by fluorescence detection after separation by HPLC. This general procedure has been used for various matrices, including runoff water (Nessel et al. 1989), marine sediments (Cannavan et al. 2000), and plasma and dung (Sommer and Steffansen 1993). Cannavan et al. (2000) provided a thorough description of the analytic process for marine sediments. The authors also noted that quality control assessment is hampered by the lack of a certified reference material for avermectins in marine sediments. The quantitation limit of the assay used by Cannavan et al. (2000) was 0.93 ng/g.

Table 2
Physical and chemical properties of avermectins

Parameter	Ivermectin	Abamectin	Emamectin benzoate
Molecular weight	875	873.11	994–1 008
K_{ow}	1 651	9 772	100 000
K_{oc}	12 660–15 700	5 300–15 700	3 485–24 176
Aqueous solubility	4 mg·L^{-1}	7.8 µg·L-1	24–320 mg·L^{-1}
Vapour pressure	< 1.5 x 10^{-9} mm Hg	NA	3 x 10^{-8} mm Hg
Photolysis in water	< 0.5 days	< 0.5 days	0.7–35.4 days
Soil half-life	93–240 days*; 7–14 days**; 91–217 days***	14–56 days	174 days

* In the laboratory, in the dark, ~22°C, in soil/feces mixtures.
** Outdoors, in summer, in soil and soil/feces mixtures.
*** Outdoors, in winter, in soil and soil/feces mixtures.

NA: Not available.

1.3 MODE OF ACTION

Despite the large number of studies that have been conducted to examine the activity of avermectins, their precise mode of action remains unclear. The prevailing model suggests that avermectins act by interfering with the functioning of neuromuscular synapses. The known anti-parasitic effects of avermectins are: 1) paralysis of the pharyngeal muscles and 2) paralysis of somatic muscles (*citations in* Feng et al. 2002). The paralysing effects on the pharyngeal muscles are associated with the interaction of avermectins with glutamate-gated chloride (GluCl) channel receptors. The physiological role of GluCl in the pharynx is to mediate the action of glutamate released from pharyngeal motorneurons. Exogenous glutamate inhibits pharyngeal pumping, which is mimicked by ivermectin (Pemberton et al. 2001). Paralysis of somatic muscles, on the other hand, is associated with gamma-aminobutyric acid (GABA)-gated chloride channel receptors (Feng et al. 2002). A common model of the action of avermectins is that they increase muscle permeability to chloride ions, in turn reducing the excitatory potential and input resistance of the tissue. In the presence of avermectins, GABA is released, binds to muscle membranes and as a result, chloride channels remain open. This negative charge is maintained at the motor neuron, and the membrane becomes hyperpolarized, blocking the signals for excitatory or

inhibitory action (Edwards et al. 2001, *citations in* Lasota and Dybas 1991). The evidence to date is contradictory, however. For example, the application of ivermectin to various preparations of insect nerve tissue can elicit different responses. The same preparation may exhibit distinct types of paralysis (flaccid, turgid, reversible and irreversible) in response to different concentrations of this drug (Jackson 1989). The variability of response has led some researchers to conclude that there are structurally and functionally diverse GABA receptor subunits (Feng et al. 2002) and that there are multiple sites of action for avermectins.

GABA is a common neurotransmitter found in most invertebrates and in the central nervous systems (CNS) of vertebrates, while GluCl is found only in invertebrates. In vertebrates, GABA receptors are located mostly in the brain. Thus, vertebrates are protected from the effects of ivermectin by the "blood-brain barrier," which is mediated by the amount of P-glycoprotein present in the brain (Marques-Santos et al. 1999). This barrier accounts for the drug's wide safety margin (or therapeutic index). However, radio-labelled ivermectin has been detected in the brain of Atlantic salmon (*Salmo salar*) administered ivermectin at normal treatment doses (Høy et al. 1990). On the other hand, arthropods have an "open" vascular system and, in insects at least, GABA functions as a neurotransmitter both within the CNS and at neuromuscular junctions in the peripheral nervous system. This may explain some of the diverse effects observed among arthropods exposed to sublethal doses of ivermectin.

The preceding model of the mode of action of avermectins provides an elegant framework to understand the majority of the observed effects of exposure in target and non-target organisms. However, not all of the observed impacts of exposure can be unequivocally explained by this model. For instance, there is evidence in the literature that avermectins can result in disruptions to endocrine systems. Treatment of dairy heifers with ivermectin has shown that it can significantly increase sexual maturation, as well as the level of the reproductive hormones IGF-I and LH (insulin-like growth factor I and luteinizing hormone) (Lacau-Mengido et al. 2000). It was not clear from this study whether ivermectin had a direct impact on the endocrine system of heifers or whether the absence of parasitism allowed treated heifers to have an energetic advantage over the untreated, but parasitized control group. Although reduced growth as a result of parasitism can impair endocrine function, the authors concluded that this could not explain all of their observations and suggested that ivermectin was potentially affecting IGF-I

levels directly. Interestingly, researchers have observed that exposure to other endocrine disruptors decreases the levels of IGF-1 in Atlantic salmon (*S. salar*) and reduces the weight of smolts (Arsenault et al. 2004). No research has yet tested for the endocrine-disrupting impacts of avermectins in any fish species.

There has been very little research that clearly separates the nutritional impacts of ivermectin treatment (i.e. indirect impacts on endocrine system) vs. direct effects on the endocrine system. GABA receptors have been identified in peripheral organs like the hypothalamus, pituitary gland and ovaries in humans and in rats (Whittier et al. 1999, Erdo et al. 1985, Schaeffer and Hsueh 1982). This has led some researchers to conclude that ivermectin can directly disrupt the endocrine system by binding to GABA receptors located on ovaries, thereby stimulating reproduction (Whittier et al. 1999). Abamectin is considered to be a potent inhibitor of reproduction in red imported fire ants (RIFA) (Glancey et al. 1982). When queens were exposed to low doses, several histological impacts on the reproductive systems were noted, including hypertrophy of the epithelial cells surrounding eggs, reduced egg production and size, abnormal clumping of chromatin in the nurse cells (pycnosis), and the absence of egg yolk within the eggs. The authors conclude that the evidence supports a direct action on the endocrine system of the RIFA queen and not simply an indirect effect of reduced feeding activity.

The best evidence that avermectins can disrupt endocrine systems comes from a study on American lobster (*Homarus americanus*). Lobsters force-fed slurry containing emamectin benzoate moulted sooner than non-exposed lobsters. Furthermore, exposed lobsters that were bearing eggs aborted their broods (Waddy et al. 2002). The authors suggest that emamectin benzoate interferes with the function of the moult-inhibiting hormone (MIH). In decapod crustaceans, MIH is produced in the medulla terminalis X-organ and is released from a sinus gland in the eyestalk. Its main function is to regulate moulting by inhibiting the secretion of ecdysteroids (Dell et al. 1999). Crustaceans progress in developing as the concentration of MIH decreases. In insects, the hormonal regulation of moulting works in the opposite direction; as the prothoracicotropic hormones increase, moulting is induced (Gilbert et al. 2002). It is interesting to note that GABA inhibits the release of other eyestalk neuropeptides in crustaceans (Sarojini et al. 2000, *cited in* Waddy et al. 2002). Most researchers who have observed the negative impacts of exposure to avermectins on insect reproduction have assumed that it was due to their impacts

on energy acquisition and hence growth and reproduction. The hypothesis of Waddy and colleagues offers another potential mechanism for these observations. However, no hypothesis concerning the mechanism of endocrine disruption by any of the avermectins has yet been tested in a laboratory study.

Developmental abnormalities, also known as *fluctuating asymmetry*, have been observed in flies exposed to ivermectin-treated feces. Clark and Ridsdill-Smith (1990) found that adults of *Musca vetustissima* (Diptera) emerging from outdoor cow pats treated with avermectin B_1 showed higher levels of fluctuating wing asymmetry. Strong and James (1993) showed that in *Scatophaga stercoraria* (Diptera) exposed to dung containing 0.0005 ppm ivermectin, there were significant differences in the symmetry of wing venation patterns. Increases in fluctuating asymmetry have been linked to developmental instability as a consequence of genomic and/or environmental stress (Parsons 1992). Although it is unclear what degree of risk wing abnormalities pose to the organism's or population's survival, it does demonstrate a previously unknown action of avermectins at the level of cell development and differentiation (Strong and James 1993).

1.4 AVERMECTIN METABOLISM

The absorption, excretion, distribution and metabolism of tritium-labelled ivermectin have been studied in livestock and rats (Chiu and Lu 1989). Regardless of administration route, ivermectin accumulates the most in the liver and fatty tissues of organisms and the least in brain tissues. The parent compound is the major component found in the liver and fat tissues, but other polar metabolites are present in these tissues as well. The manner in which ivermectin is metabolized by vertebrates differs depending on the mode of administration, some formulations providing a slower release of the drug than others (Hennessy and Alvinerie 2002).

Avermectins are poorly metabolized by the target organism and are mostly excreted via feces (less than 2% is excreted via urine). Halley et al. (1989a) measured the proportion of avermectins in the feces of treated animals and found that the proportion of ivermectin ranged from 23–43% in swine, 39–45% in cows and 61–69% in sheep. It should be noted that these authors measured the levels of ivermectin in seven-day-old feces and therefore might have missed the peak in ivermectin concentration, which can happen on the second or third day post

dosing (Herd et al. 1996). Other researchers have measured concentrations in feces at up to 80–98% of the initial administered dose (Herd et al. 1996; Jackson 1989). Excretion patterns are also affected by the formulation of the administered avermectin (subcutaneous injection, pour-on, slow-release bolus) (Herd et al. 1996). For pour-on formulations, which are administered at a higher dose (0.5 mg/kg), the majority of the total dose is excreted two days post dosing. Excretion peaks on the third day for subcutaneous injection and is a much lower percentage of the total initial dose (Herd et al. 1996).

The combination of their physical/chemical properties (non-volatile, low water solubility and strong affinity for lipids and organic matter) with the high excretion rate of the parent compound from treated animals has raised concerns that toxic levels of avermectins are entering and persisting in various environmental compartments.

2 Fate in the Environment

2.1 CONCENTRATIONS AND PERSISTENCE IN ENVIRONMENTAL COMPARTMENTS

To understand the potential environmental fate of avermectins, it is first necessary to assess their probable concentration in various environmental compartments, which will depend initially on the method of application, the dose applied and the frequency of dosing. The physical/chemical properties of avermectins indicate that, once they have entered the environment, they can persist for extended periods of time at concentrations high enough to exert toxic impacts. To date, pasture ecosystems have been of greatest concern. In terrestrial systems, the entry of ivermectin into the environment is through livestock excretion on pasture soils. Ivermectin enters marine systems in the feces of farmed salmon, as well as through uneaten food that settles in sediments.

Research into the persistence of avermectins in the environment has produced inconsistent results. Initial environmental assessments of ivermectin indicated that, in soil/feces mixtures under summer field conditions, photodegradation and aerobic metabolism would result in a degradation half-life of 2 to 8 weeks (Halley et al. 1989a). However, Lumaret et al. (1993) reported that ivermectin in dung pats deposited on fields at the end of spring in Spain could no longer be measured after six days, while Sommer and Steffansen (1993) reported half-lives of 2.5 to 3 days (pour-on and injection treatments of cattle). In contrast, Madsen et al. (1990) reported that ivermectin remained active (as measured by toxic impacts on dung fauna) in dung pats for two months and Herd et al. (1996) reported measurable concentrations of ivermectin up to 50 days post treatment. Although it is difficult to compare these results because they were conducted using different experimental designs, at different times of the year, and in various climate types, it is clearly possible for avermectins to persist in the environment for a considerable period of time.

Table 3
Persistence of ivermectin in dung

Dose (mg/kg body weight)	Administration route	Maximum concentration (mg/kg wet weight)	Days after treatment that maximum concentration measured	Days until lowest concentration or no IVM measured	Reference
0.2	Subcutaneous injection	0.42	5	12	Lumaret et al. 1993
0.5	Pour-on	1.35	1	14	Sommer and Stefanson 1993
0.2	Subcutaneous injection	0.58	2	13.5	Sommer and Stefanson 1993
12 (d^{-1})	Bolus	NA	11	100	Wall and Strong 1987
0.5	Pour-on	NA	10*	14	Floate 1998
0.2	Subcutaneous injection	0.0626 ppm**	3	NA	Nessel et al. 1989
12.7 (d^{-1})	Bolus	0.82	24.5	30	Herd et al. 1996
0.5	Pour-on	2.57	2	20	Herd et al. 1996
0.2	Subcutaneous injection	0.21	3	20	Herd et al. 1996

* Concentration not reported.
** This is the only concentration reported, thus it is not necessarily a reflection of the peak.

NA: Not available.

Researchers have attempted to estimate the environmental burden (predicted environmental concentration, PEC) of ivermectin that accumulates in pasture ecosystems by developing simple models, using parameters based on standard agricultural practices. PECs estimated by Halley et al. (1989b) indicate that feedlot cattle and swine agri-systems would produce the highest concentration of ivermectin in pasture soils (0.2 ppb) after the manure had been ploughed into the soil. This model assumes that all ivermectin was present as the parent compound, that all of it was excreted at once, and that it was not degraded during the feedlot or pasture periods.

Montforts et al. (1999) developed a more realistic PEC model by including the effects of metabolism and the kinetics of excretion of ivermectin in cattle. Their model output indicated a PEC for dairy and beef cattle that decreased from 1.39 and 1.16 mg ivermectin/kg manure to < 0.0004 and < 0.0003 mg ivermectin/kg manure (dairy and beef, respectively) over 11 days post

treatment. Their model outputs were similar to the concentration of ivermectin measured in dung under field conditions.

2.2 IMPACTS ON TERRESTRIAL FAUNA

Various lethal and sublethal impacts have been observed in non-target organisms exposed to avermectins. Most of this research has focused on exposure of fauna to livestock dung in agricultural pastures. However, there is a growing body of literature that reflects the negative consequences of exposure in marine organisms.

2.2.1 Lethal impacts

A wide range of terrestrial invertebrates, such as dipterans, coleopterans, hymenopterans, lepidopterans, annelids and acarids, have been tested for their responses to avermectins. The results of these studies show that even at low levels of exposure, avermectins can be lethal (Table 4). Laboratory bioassays have demonstrated that invertebrates are susceptible to ivermectin at low levels of exposure (e.g. LC_{50}[2] = 0.036 ppm for the yellow dung fly) (Strong and James 1993). Some of these bioassays may also underestimate lethality, as the duration of the tests (24–72 hrs) may not be long enough; avermectins are slow acting, with death sometimes occurring many days after exposure.

Field trials with natural and artificial pats demonstrate similar lethal effects. Pats produced by cattle treated with avermectins tend to show a significantly reduced number of total live larvae, pupae, or adults, most notably among larval dipterans and coleopterans (Table 4). These results have been confirmed by field trials examining impacts on the diversity of whole dung pat communities (Table 4). At ivermectin concentrations of 0.5 mg/kg, there were significant changes in the communities in and immediately below the pats (McCracken and Foster 1993). Ivermectin appeared to inhibit larval development and prevent pupation. Krüger and Scholtz (1998a, b) examined the long-term impact of ivermectin exposure on community diversity in dung and found that exposure to ivermectin could reduce the diversity of insect species and increase the dominance of certain species for three months. However, these responses

[2] LC_{50}: The concentration of a toxicant that is lethal to 50% of a test population over a specific period of time.

were altered by climatic conditions; during drought, impacts on diversity were significant, but during a rainy year, there were no significant differences in any community measures.

The activity of insects associated with dung pats is a principal driver of their degradation and the dispersal of the nutrients they contain. Exposure to ivermectin in dung pats reduces insect activity. Several researchers have observed that the degradation rate of treated dung pats is significantly slower than that of non-treated pats (Wall and Strong 1987, Floate 1998). Results of dung pat degradation studies remain equivocal. Degradation is influenced by factors other than insect activity, such as climate and precipitation, which may therefore play a role in the discrepancies among the studies.

The lethal effects of ivermectin can persist in dung pats for extended periods of time. Madsen et al. (1990) observed that ivermectin-treated pats were lethal to cyclorrhaphan Diptera for 30 days and to nematoceran Diptera for 10 days. Wardhaugh and Rodriguez-Menendez (1988) also showed that ivermectin-treated dung remained lethal to dipterans for up to 32 days.

2.2.2 Sublethal impacts

Researchers have argued that the lack of consistent patterns across taxa and studies indicates that exposure to avermectins would be inconsequential in the long term, as sufficient numbers of invertebrates would survive to maintain populations (McKellar 1997). These assertions are based on assessments of the number of live larvae and adults in treated dung and the estimated amount of avermectin-free dung available to invertebrate populations. Others have argued that this underestimates the potential dangers of exposure because sublethal responses are ignored (Strong 1993, Strong and James 1993). Just because an organism is alive does not necessarily mean that it will successfully mate, reproduce and contribute to the long-term viability of its population.

Among the various sublethal responses that have been noted as a consequence of exposure to avermectins are reduced growth (inhibited larval and pupal development, reduced emergence, or smaller larval head capsule widths), alterations in reproduction (reduced brood ball production, egg production, altered mating behaviour, and ovarian abnormalities), disruption of water balance, and reduced ability to moult normally. In addition, some researchers have noted developmental abnormalities in flies exposed to dung from cattle treated with ivermectins

(Table 4). These abnormalities include induction of fluctuating asymmetry as measured by wing venation patterns. In contrast, earthworms show a very high degree of tolerance for exposure to avermectins, with no effects on survival rates or reproduction (Svendsen et al. 2002).

Table 4
Lethal and sublethal responses in terrestrial organisms

Test organism	Time	Parameter	Effect	Reference
INSECTS				
Coleoptera				
Diastellopalpus quinquedens	28 days	Development, mortality, morphology of head capsules	Reduced % of brood masses with live larvae and reduced larvae or pupae on day 2	Sommer et al., 1993
Euoniticellus fulvus	3 weeks and 10 days	Fecundity, survival and ovarian development	Reduced survival and emergence on days 1, 10 and 32; unable to accumulate fat and develop normal oocytes	Wardhaugh et al., 1993
E. fulvus	30 days	Presence/absence	Increased number of beetles in treated pats	Lumaret et al., 1993
E. intermedius	56 days	Emergence, development, survival, fecundity and fertility	Reduced number of brood balls on day 3; reduced emergence days 2 to 14; 0 to 3% survival days 2 to 14; development time prolonged days 1 to 28; adult fertility reduced day 1	Krüger and Scholtz, 1997
Onitis alexis	56 days	Emergence, development, adult size	Reduced emergence days 2 to 7; prolonged development days 1, 2, 4 to 21; no difference in adult live mass	Krüger and Scholtz, 1997
Onthophagus gazella	28 days	Development, mortality, morphology of head capsules	Reductions in development and mortality on days 2 and 8; reduced head capsule width	Sommer et al., 1993
O. taurus	15 days	% dung pat dispersal, number of beetles/pat	Reductions on days 7 and 10 post treatment	Dadour et al., 1999
Diptera				
Musca domestica	30 days	Mortality	Increased mortality for 20 days	Madsen et al., 1990
M. nevilli	56 days	Development, survival, emergence, reproduction	Development delayed 4 weeks; 0% larval survival and emergence 4 weeks; reduced fertility	Krüger and Scholtz, 1995
M. vetustissima	8 hours	Mortality and fluctuating asymmetry	0% survival days 1 to 4; altered wing asymmetry	Wardhaugh et al., 1993

Test organism	Time	Parameter	Effect	Reference
Neomycia cornicina	30 days	Mortality and development	Significant decreases days 9 to 23 only	Lumaret et al., 1993
Lucilia cuprina	6 days	Mortality, mating and reproduction	Fewer mating attempts, longer mating duration, no difference in % mating; delayed ovipositioning, increased mortality	Cook, 1993
	14 days and 6 days	Mortality, fecundity and ovarian development	Increased mortality; fewer gravid females, and reduced oocyte production day 1; reduction in mature oocyte retention, no effect on egg viability	Mahon et al., 1993
Scatophaga stercoraria	24 hours	Mortality (EC_{50})	0.051 ppm (wet weight)	Strong and James, 1993
	48 hours	Mortality (EC_{50})	0.036 ppm (wet weight)	Strong and James, 1993
	10 days	Emergence (EC_{50})	0.001 ppm	Strong and James, 1993
	10 days	Pupariate (EC_{50})	0.015 ppm	Strong and James, 1993
	10 days	Fluctuating asymmetry	0.0005 ppm	Strong and James, 1993
OLIGOCHAETA				
Eisenia foetida	28 days	Mortality (LC_{50})	315 ppm	Halley et al., 1989a
	14 days	Mortality (LC_{50})	15.8 ppm	Gunn and Sadd, 1994
	14 days	Growth (EC_{50})	4.7 ppm	Gunn and Sadd, 1994
	14 days	Cocoon production (EC_{50})	4.0 ppm	Gunn and Sadd, 1994
Lumbricus terrestris	24 weeks	Survival and growth	No effect	Svendsen et al., 2002
Whole dung community		Diversity	Significant differences in community in and under pats	McCracken and Foster, 1993
	119 days	Dung degradation; dipteran and coleopteran diversity	Decrease in number of larvae; no effect on number of adults	Barth et al., 1993
	3 months	Evenness and diversity	Lower in treated and natural pats after 3 months and after 2 months in artificial pats	Krüger and Scholtz, 1998a
	3 months	Evenness and diversity	Natural pats: reduced diversity first 7 days post treatment and 3 months post treatment	Krüger and Scholtz, 1998b
	30 days	Development	Inhibited development of Cyclorrhapha dipterans for 30 days, Nematocera dipterans for 10 days; no effect on earthworms	Madsen et al., 1990

Studies that tracked sublethal responses over time have shown that the impacts of exposure to dung from treated cattle last for several days to several weeks.. For example, dung from cattle treated with ivermectin prevented the emergence of adult Euoniticellus intermedius (Diptera) for 2 to 7 days post treatment, and prevented the development of E. intermedius larvae for 28 days after injection (Krüger and Scholtz 1997). Flies that did emerge successfully from treated pats had reduced fertility for 5 to 8 weeks after treatment (Krüger and Scholtz 1995). Floate (1998) also observed that emergence from treated pats was reduced for 12–16 weeks post treatment.

It is also interesting to note that susceptibility to lethal or sublethal doses of avermectins is highly variable among taxa, even those that are very closely related. For example, when exposed to dung from cattle treated with a subcutaneous injection of ivermectin, both *Onthophagus gazelle* and *Diastellopalpus quinqueden* (Coleoptera: Scarabaeidae) showed incomplete development of brood masses, reduced number of live larvae in exposed dung, and reduced head capsule width (Sommer et al. 1993). However, *D. quinqueden* was far less susceptible than *O. gazelle,* despite the fact that these two species are so closely related that researchers at one time thought *D. quinqueden* was a subgenus of *O. gazelle* (Sommer et al. 1993). In general, researchers have found that dipteran species from the infraorder Cyclorrhapha and Nematocera tend to be more sensitive to exposure than dipterans from other orders.

2.3 IMPACTS ON AQUATIC FAUNA

The aquaculture industry began using ivermectin as an alternative chemotherapeutic treatment for ectoparasitic copepods, also known as sea lice. Its use in the aquaculture industry is "off-label"; use in fish is not recommended by the manufacturer, but veterinarians are still allowed to prescribe food treated with ivermectin under "emergency situations." The ecotoxicological effects and persistence of ivermectin in terrestrial ecosystems raised significant concerns among researchers and the public about its use in marine environments (Davies and Rodgers 2000). Subsequently, studies were undertaken to measure the potential impacts on target and non-target fauna in marine systems.

2.3.1 Lethal impacts

Information provided in aquaculture literature is generally restricted to lethal impacts. Only one study has measured *in situ* concentrations of ivermectin in sediments near a fish-farming operation, and only one study has examined impacts on *in situ* infaunal organisms living underneath these farms (Costelloe et al. 1998). Most information on impacts has been gathered through single or multi-species bioassays and exposure has generally been via dissolved ivermectin, except for a small number of studies that have directly compared food versus waterborne exposure.

2.3.2 Impacts on target animals

Atlantic salmon (*Salmo salar*) is one of the most important aquaculture fishes in the world, therefore much research has focused on maintaining its health in captivity. The difference between treatment dosage and toxic effects of ivermectin in Atlantic salmon is very narrow (Palmer et al. 1987). A commonly recommended treatment dose of ivermectin is 0.05 mg/kg, given twice weekly in feed, with no treatments in winter. However, the 96 h LD_{50} was determined to be 0.5 mg/kg (Palmer et al. 1987) with a 96 h LC_{50} set at 17 µg/L (Kilmartin et al. 1996). Symptoms of ivermectin toxicity in Atlantic salmon include loss of appetite, dark skin coloration, lethargy and erratic swimming behaviour (Palmer et al. 1987). These symptoms can occur in fish that have been treated with doses as low as 0.05 mg/kg. As with terrestrial invertebrates, the impacts of ivermectin in fish vary from one species to another. The sensitivity of Atlantic salmon is relatively equal to that of brown trout (*Salmo trutta*), but less than that of rainbow trout (*Salmo gairdneri*) (Table 5). When administered to rainbow trout at a dose of 1 µg/kg, exposure to ivermectin resulted in a mortality rate of 38% (*cited in* Katharios et al. 2001). No mortality was reported in bream (*Sparus aurata*) exposed to oral doses ranging from 100 to 800 µg/kg (Katharios et al. 2001). The fish had lower hematocrit values at all treatment doses and exhibited lethargy, appetite loss and skin darkening at the highest treatment dosages.

The half-life of ivermectin administered to Atlantic salmon at the recommended dose is 120 degree-days [3] (Roth et al. 1993). In contrast, when bluegill sunfish (*Lepomis macrochirus*)

[3] Degree-days refer to the amount of time required to complete metabolic processes that are temperature dependent. They are calculated by multiplying the number of days required by the appropriate temperature. For

were exposed to abamectin (0.99 µg/L) for 28 days, the fish cleared up to 95% of the accumulated abamectin with a depuration half-life of 3.3 days and a depuration rate of 0.21/d. The measured bioconcentration factor (BCF)[4] for the bluegill was 56 L/kg (Van den Heuvel et al. 1996). The authors argue that although the K_{ow} of abamectin indicates that it should be highly lipophilic, the compound's high molecular weight limits its membrane permeability.

2.3.3 Impacts on non-target marine organisms

Very little is known about the lethal and sublethal impacts of avermectin exposure on non-target aquatic organisms. The available data on ivermectin toxicity demonstrates a wide range of species sensitivity to the compound, with crustaceans apparently more sensitive than other organisms (Table 5). Bioassays with dissolved ivermectin have shown toxic thresholds as low as 0.026 µg/L (48 h LC_{50}) (Grant and Briggs 1998) and 0.07 µg/kg (96 hr LC_{50}, Davies et al. 1997) for the mysid *Neomysis integer*. Interestingly, benthic nematodes seem relatively resistant to ivermectin exposure, exhibiting 72 h LC_{50} >10 000 µg/L (Grant and Briggs 1998). Mussels exposed to dissolved ivermectin at a concentration of 6.9 µg/L accumulated a maximum concentration of 5.2 mg kg^{-1}. The authors estimated a depuration half-life of 22 days (235 days) and a BCF of 750 µg/kg. However, most of these studies have exposed test organisms to dissolved ivermectin, which does not reflect the more likely environmental exposure route, sediments.

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example, in salmon, the incubation process to get a salmon egg to the "eyed" stage takes 35 to 45 days at temperatures between 6 and 8ºC, which results in approximately 250 to 350 degree-days.

[4] Bioconcentration factors (BCFs) are used to relate pollutant residues in aquatic organisms to the pollutant concentration in ambient waters. According to the EPA, "the BCF is defined as the ratio of chemical concentration in the organism to that in surrounding water. Bioconcentration occurs through uptake and retention of a substance from water only, through gill membranes or other external body surfaces."

Table 5
Results of standard toxicity bioassays (lethal and sublethal endpoints)

Test organism	Time	Compound*	Route**	Parameter	Dose	Reference
VERTEBRATES						
FISH						
Anguilla anguilla	24 h	IVM	D	LC_{50}	0.2 ppm	Geets et al., 1992
Lepomis macrochirus	96 h	IVM	D	LC_{50}	4.8 ppb	Halley et al., 1989a
Salmo salar	96 h	IVM	I	LC_{50}	500 ppb	Kilmartin et al., 1996
	96 h	IVM	D	LD_{50}	17 ppm	Halley et al., 1989a
Salmo gairdneri	96 h	IVM	D	LC_{50}	3 ppb	Kilmartin et al., 1996
Salmo trutta	96 h	IVM	I	LC_{50}	300 ppb	Wislocki et al., 1989
Cyprinodon variegatus	96 h	ABA	D	LC_{50}	15 ppb	
Ictalurus punctatus	96 h	ABA	D	LC_{50}	24 ppb	
Cyprinus sp.	96 h	ABA	D	LC_{50}	42 ppb	
Sparus aurata	35 d	IVM	I	LC_{50}	0% mortality	Katharios et al., 2002
MARINE INVERTEBRATES						
CRUSTACEANS						
Anostraca						
Artemia salina	24 h	IVM	D	LC_{50}	> 300 ppb	Grant and Briggs, 1998
Isopoda						
Sphaeroma ragicauda	96 h	IVM	D	LC_{50}	348 ppb	
Decapoda						
Crangon septemspinosa	24 h	IVM	F	LC_{50}	13.1 ppm	Burridge and Haya, 1993
	48 h	IVM	F	LC_{50}	9.7 ppm	
	97 h	IVM	D	LC_{50}	> 21.5 ppb	
Palaemonetes varians	96 h	IVM	D	LC_{50}	54 ppb	Grant and Briggs, 1998
Penaeus duorarum	96 h	ABA	D	LC_{50}	1.6 ppb	Wislocki et al., 1989
Callinectes sapidus	96 h	ABA	D	LC_{50}	153 ppb	
Carcinus maenas	96 h	IVM	D	LC_{50}	957 ppb	Grant and Briggs, 1998
Amphipoda						
Corophium volutator	10 d	IVM	S	LC_{50}	0.18 ppm	Davies et al., 1998
Mysidacea						
Neomysis integer	48 h	IVM	D	LC_{50}	0.026 ppb	Grant and Briggs, 1998
Mysidopsis bahia	96 h	ABA	D	LC_{50}	0.022 ppb	Wislocki et al., 1989
Neomysis integer	96 h	IVM	D	LC_{50}	0.07 ppb	Davies et al., 1997
ECHINODERMS						
Asteroida						
Asterias rubens	10 d	IVM	S	LC_{50}	23.6 ppm	Davies et al., 1998
ANNELIDS						
Polychaeta						
Arenicola marina	10 d	IVM	S (dry)	LC_{50}	23.0 ppb	Grant and Briggs, 1998
	10 d	IVM	S (dry)	LC_{50}	0.02 ppm	Thain et al., 1997
Nereis (Hediste) diversicolor	96 h	IVM	D	LC_{50}	7.75 ppb	Grant and Briggs, 1998

Test organism	Time	Compound*	Route**	Parameter	Dose	Reference
MOLLUSCS						
Bivalvia						
Crassostrea virginica	96 h	ABA	D	LC_{50}	430 ppb	Wislocki et al., 1989
Crassostrea gigas:						
– Larvae	96 h	IVM	D	LC_{50}	80–100 ppb	Kilmartin et al., 1996
– Spat	96 h	IVM	D	LC_{50}	600 ppb	
Mytilus edulis	96 h	IVM	D	LC_{50}	400 ppb	
Pecten maximus	96 h	IVM	D	LC_{50}	300 ppb	
Tapes semidecussata:						
– Larvae	96 h	IVM	D	LC_{50}	380 ppb	
– Spat	96 h	IVM	D	LC_{50}	460 ppb	Kilmartin et al., 1996
Gasteropoda						
Hydrobia ulvae	96 h	IVM	D	LC_{50}	> 10 000 ppb	Grant and Briggs, 1998
Potamopyrgus jenkinsii	96 h	IVM	D	LC_{50}	< 9 000 ppb	Grant and Briggs, 1998
Littorina littorea	96 h	IVM	D	LC_{50}	> 1 000 ppb	
	96 h	IVM	D	LC_{50}	580 ppb	Kilmartin et al., 1996
Nucella lapillus	96 h	IVM	D	LC_{50}	390 ppb	
Patella vulgata	96 h	IVM	D	LC_{50}	600 ppb	
NEMATODES	96 h	IVM	D	LC_{50}	> 10 000 ppb	Grant and Briggs, 1998
FRESHWATER INVERTEBRATES						
CRUSTACEANS						
Cladocera						
Daphnia magna	48 h	IVM	D	LC_{50}	0.025 ppb	Halley et al., 1989a
	48 h	IVM, metabolite 1	D	LC_{50}	0.4 ppb	
	48 h	IVM, metabolite 2	D	LC_{50}	> 17 ppb	
	48 h	IVM, leachate	D	LC_{50}	a.d.	
	48 h	IVM	S	CE_{50}	39 ppb	Halley et al., 1993
	48 h	IVM, dung leachate	D	LC_{50}	6.5 ppb	
	48 h	ABA	D	LC_{50}	0.34 ppb	Wislocki et al., 1989
Amphipoda						
Gammarus duebeni and *G. zaddachi*	96 h	IVM	D	LC_{50}	0.033 ppb	Grant and Briggs, 1998
MOLLUSCS						
Gasteropoda						
Biomphlaria glabrata	24 h	IVM	D	LC_{50}	30 ppb	Matha and Weiser, 1988

* Compound refers to the type of avermectin used in the experiment; IVM: ivermectin; ABA: abamectin.

** Route refers to route of exposure to test organisms; D: dissolved state; I: intubation or injection; F: food; S: sediment.

Sediment bioassays indicate that the polychaetes *Arenicola marina* (Thain et al. 1997) and *Hediste diversicolor* (Collier and Pinn 1998), and the amphipod *Corophium volutator* (Davies et al. 1998, Collier and Pinn 1998) are sensitive at low levels of exposure (Table 5). Exposure to ivermectin in sediments also seems to selectively reduce the abundance of individuals in small size-classes of *C. volutator* (Collier and Pinn 1998). Black et al. (1997) incubated marine intertidal sediment cores with different concentrations of ivermectin and determined that the toxic threshold for polychaetes (mostly *Capitella* spp.) was between 8.1 and 81 μg/m. In a similar experiment, Collier and Pinn (1998) collected cores containing benthic invertebrates from the intertidal zone and exposed them to various concentrations of ivermectin. They determined that the community toxic threshold was between 8.0 and 80 mg ivermectin per m2. It should be noted that a field study investigating the benthic community underneath a fish farm using ivermectin for nine years found no effect of exposure on the polychaete community (Costelloe et al. 1998), despite measuring concentrations of up to 6.8 ng/g of ivermectin in the sediments directly underneath the fish nets (Cannavan et al. 2000).

Ivermectin exposure has also been shown to have significant sublethal impacts on marine organisms. Exposure to 20 mg/kg significantly reduced the ability of *Asterias rubens* to right itself. Reductions in the rate of cast production by *Arenicola marina* were measured at all test concentrations (≥ 0.006 mg/kg sediment, dry weight) and prior exposure to ivermectin significantly reduced *A. marina's* ability to rebury itself in clean sediment (Thain et al. 1997). Additionally, exposure to emamectin benzoate induced premature moulting and abortion of broods in the American lobster *(Homarus americanus*), which is indicative of impacts on the lobster's endocrine system (Waddy et al. 2002).

2.3.4 Impacts on non-target freshwater organisms

The initial environmental assessments of ivermectin and abamectin concluded that, in general, they did not pose a significant risk to freshwater environments (Halley et al. 1989a, Nessel et al. 1989, Wislocki et al. 1989). As a result, very few studies have been undertaken to examine the adverse impacts of exposure to avermectins on freshwater organisms. To date, however, *Daphnia magna* has the lowest LC_{50} (0.025 μg/L) of all organisms tested. One freshwater species, the oligochaete *Lumbriculus variegates*, has been tested for lethal and

sublethal effects of exposure to abamectin. It was found that concentrations greater than 560 nmol were toxic, but at concentrations of 300 nmol, the oligochaete's ability to move, swim and crawl was significantly inhibited (Ding et al. 2000). Fourteen days of exposure to dissolved abamectin caused significant reductions in the number of Ephemeroptera larvae (particularly *Baetis* spp.), Coleoptera larvae, Hemiptera nymphs and chironomid larvae (Ali et al. 1997). Dissolved ivermectin was lethal to the euryhaline amphipods *Gammarus duebeni* and *G. zaddachi*, at concentrations as low as 0.033 µg/L (Grant and Briggs 1998). The freshwater snail *Biomphalaria glabrata* has also been tested for acute toxicity and its LC_{50} was determined to be 30 ppb. The exposure pathway in this study was the water column and therefore the study likely underestimated the potential toxicity of avermectins to this organism (Matha and Weiser 1988). Dissolved abamectin is lethally toxic at doses ranging from 9.6 to 42 µg/L in freshwater fish (Table 5). Some sublethal responses have also been noted in freshwater fish. Toovey et al. (1999) found that ivermectin caused a significant, dose-dependent reduction in gill oxygen consumption at concentrations of > 1.21 µg/mL, with an EC_{50} of 2.15 µg/mL. Ivermectin reduced gill respiration by up to 72% at a concentration of 11.2 µg/mL.

Few studies have sought to quantify the actual concentration of avermectins that reach aquatic sediments. However, Cannavan et al. (2000) found that 31% of ivermectin administered to farmed Atlantic salmon during a treatment cycle accumulated in the top 9 cm of sediments in the immediate vicinity of fish cages. The highest concentration measured was 6.8 ng/g directly underneath the cages, but sediment concentrations exceeded the detection limit up to 30 m away from the cages. Davies et al. (1998) found that 100-day-old sediment still exerted toxic impacts on benthic invertebrates. Their measurements indicated that only 30% of the ivermectin had degraded over that period, and therefore the half-life of ivermectin in marine sediments would be in excess of 100 days. This finding agrees with the measured half-life of emamectin benzoate in intertidal areas (150 days; SPAH 2002). Whether or not avermectins would persist for similar periods of time in freshwater systems is unknown.

3 Agriculture and Avermectins in Quebec

3.1 QUEBEC LIVESTOCK AND MANURE MANAGEMENT

Agriculture is the largest source of avermectins in the environment. The total amount of avermectins entering the environment is a product of livestock type, the total amount of manure produced, the levels of parasitism (perceived or measured), and manure management practices.

Livestock farming in Quebec is characterized by medium- (3–80 animal units[5] per hectare) to high-density (80.1–1070 animal units per hectare) farming operations (Beaulieu 2001). Dairy farms, followed by hog farms, account for the majority of farms in Quebec, (MENV 2003a), and hence the greatest amount of manure production and potentially the largest pool of anthelmintic use. There are more pigs than cattle in Quebec (Table 6). Nevertheless, cattle contribute more to total manure production in Quebec than pigs, owing to their larger body size (Table 7). Most of this livestock production occurs in southern Quebec, primarily in the Chaudière-Appalaches, Monterégie and Centre-du-Québec regions.

Manure is managed in either liquid or solid form. Solid manure systems include material like hay or bedding from confinement areas in addition to feces and urine. Liquid manure (slurry) consists of feces, urine and water used during production (e.g. water used to clean out confinement pens or animals or spillover from drinking water). Storage of these two types of manure differs due mostly to the difference in water content. The majority of manure from Quebec's pig herd is managed as liquid manure, mainly (74%) in open tanks. Manure from beef in Quebec is managed as solid manure and stored as an open pile on the ground without a roof (Statistics Canada 2003). Manure from Quebec's dairy herd is managed either in liquid or solid form (46.2% stored as liquid, 53.8% stored as solid). In small dairy herds (less than 81 heads), the majority of manure is stored as an open pile on the ground.

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[5] The concept of animal units, originally developed in the United States in the 1960s, is based on the number of animals that would produce the 73 kilograms of nitrogen required to fertilize one acre of corn for one year. The number of animals of a given kind in one animal unit is expressed as a coefficient. One cow, for example, equals approximately one animal unit, while four sows will be required for one unit (see the Statistics Canada publication *Distribution and Concentration of Canadian Livestock*).

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Table 6
Total number of livestock heads in Quebec

Administrative region	Pigs	Cattle	Sheep	Horses
Bas-Saint-Laurent	172 800	113 600	72 100	
Saguenay–Lac-Saint-Jean, Côte-Nord	11 400	58 300	15 600	
Quebec City	83 600	38 700	3 600	
Mauricie	159 400	63 500	4 900	
Eastern Townships	271 000	133 500	23 600	
Montreal, Laval, Laurentians	29 500	42 000	5 200	
Outaouais	6 500	59 600	7 300	
Abitibi-Témiscamingue, Nord-du-Québec	12 000	60 400	18 900	
Gaspésie–Îles-de-la-Madeleine	–	10 600	8 400	
Chaudières-Appalaches	1 302 700	235 800	15 700	
Lanaudière	294 800	44 700	7 300	
Montérégie	1 428 500	252 100	23 600	
Centre-du-Québec	508 000	197 200	19 000	
TOTAL	4 280 200	1 310 000	225 200	53 476

Source: ISQ, 2002a, 2002b, 2002c.

Table 7
Estimated annual production of manure, by livestock type, in Quebec

	Type of livestock			
	Cows	Pigs	Sheep	Horses
Annual manure production (kg)	15 197 130 875	5 872 184 605	149 600 360	443 075 398

Note: See Appendix 2 for calculations.

However, storage of manure in larger herds (greater than 81 heads) is approximately equally split between solid and liquid storage systems (Statistics Canada 2003). Liquid manure storage systems differ in their capacity. The majority of liquid manure has a total storage capacity of 250 to 400 days. Equivalent data for solid manure is not available. The differences in manure management are important with respect to the potential for avermectins to cause negative environmental impacts. The storage time of liquid manure will likely reduce the concentration of

avermectins in the slurry over time. Given that cattle produce the majority of manure, which is mostly stored as an open pile on the ground, there is likely a greater risk of environmental impacts from the use of avermectins in Quebec's cattle industry.

3.1.1 Cattle

Quebec is Canada's largest producer of dairy cattle, which is reflected in the proportion of dairy cattle in the province's total cattle herd (Appendix 1). In 2002, there were 1 310 000 cows in Quebec, 79% of which were part of the dairy herd. However, the number of cattle in Quebec has been decreasing steadily in past decades (MENV 2003a). Since 1971, the Quebec dairy herd has decreased by approximately 57% (MENV 2003a).

Most of the dairy herd is raised in the Chaudières-Appalaches, Montérégie and Centre-du-Québec regions (Appendix 1). Adult dairy cows and veal calves make up the majority of the Quebec herd (Appendix 1A). Dairy cattle spend the majority of their lives in individual or group pens, depending on their age (Rew and Vercruysse 2002). For example, newborn dairy cows are kept in confinement for their first year and usually are not put out to pasture until at least their second year or until they reach maturity (Caldwell et al. 1998).

The 2002 agricultural census indicated that there were 274 500 beef cattle in Quebec (ISQ 2002a). The majority of beef cattle are raised in the Chaudières-Appalaches, Outaouais and Centre-du-Québec regions. Beef cattle graze on pasture from the time they are calves until they reach a weight of 225 to 275 kg. At this point, they are weaned and fed a forage-based diet until they reach a weight of about 410 kg. Cattle are then moved to a feedlot, where they will stay until they reach market weight and are ready for slaughter. Typically, cattle will remain in a feedlot for 60 to 120 days.

Dairy and beef cattle account for 68% of Quebec's total manure production (MENV 2003a). However, as the number of cattle being raised in Quebec decreases, so does their contribution to the production of manure. This decline is expected to continue into the near future (MENV 2003a), as the pork industry continues to expand. There are two principal forms of storage for manure: liquid manure, which includes all of the liquid used to wash down confinement stalls, drinking water, feces and urine; and solid manure storage, which includes feces, urine and any organic material put in stalls (e.g. hay). A little over half (53.8%) of the

manure produced by the dairy herd is stored in solid storage systems, with approximately 20% being stored as an open pile on the ground without a roof. In the beef industry, 85.6% of manure is kept in solid storage systems, with 45% of the manure production being stored as an open pile on the ground without a roof (Statistics Canada 2003).

3.1.2 Parasitism in the Quebec cattle herd

Gastrointestinal nematode infections have significant negative impacts on the productivity and thus profitability of cattle (Sanchez et al. 2002). It is in the best financial interest of producers to maintain the health of their herds. For example, the use of eprinomectin in Quebec dairy cows can consistently increase daily milk production by 0.94 kg per day in the first six months of lactation (Nødtvedt et al. 2002).

In Quebec, *Ostertagia, Cooperia*, and to a lesser extent, *Nematodirus* are the most common gastrointestinal nematode genera infecting dairy and beef cattle (Ranjan et al. 1992; Caldwell et al. 2002). Cattle become infected with parasites that are present in the feces of infected cattle or parasites that have overwintered in pastures (Ranjan et al. 1992). Fecal egg counts of parasites in adults are lowest in the fall just after housing and then rise slowly over the course of the winter to peak just after turnout (Ranjan et al. 1992). The opposite pattern is true for calves; fecal egg counts are lowest in spring just after turnout and rise slowly over the course of the grazing season (Ranjan et al. 1992). The first grazing season for a young cow is considered to be the time of highest risk for transmission of parasites. Most herds therefore require a routine and regular treatment program for young calves from weaning to at least eight months of age.

Generally, avermectins are administered to livestock at different times of the year, with frequency depending on the management choices of the farmer and the frequency and type of infection. Typically, animals are targeted for anthelmintic control during their first grazing season (Vercruysse and Dorny 1999). Treatment can take the form of suppressive, evasive, strategic or therapeutic approaches (Forbes 1993). Strategic programs use anthelmintics early in the season to prevent infection by adult worms that will contaminate the pasture with their eggs. This approach may require several applications (Forbes 1993). Evasive strategies allow the young cattle to graze a pasture early in the season until the level of infective larvae is high in the pasture. Cattle are then treated with an anthelmintic to remove existing burdens and transferred to a parasite-free

pasture. In therapeutic strategies, farmers wait until infection occurs before any action is taken. Drugs are usually administered in the second half of the grazing season. Regardless of strategy, a dose is administered at the end of the grazing season (in some cases, this may be the only dose administered). Treatment of second-season grazing animals may be undertaken, but dosing frequency is generally lower. Adult dairy and beef cattle are rarely treated, although the introduction of an avermectin (eprinomectin) that does not accumulate in the milk of lactating dairy cattle may change this. Finally, for some formulations of ivermectin, the manufacturers' labels recommend that all cattle in the herd be treated, not just those that are infected.

In a study of 188 dairy herds in seven regions of Quebec, Caldwell et al. (2002) found that 93% of herds tested positive for gastrointestinal nematodes and that the level of infection across herds was approximately equal. The study also found that 68% of heifers and 32% of cows were treated with an anthelmintic (type not identified). This level of anthelmintic treatment was confirmed in a previous survey that found that 74% of Quebec dairy farmers treated their cattle with an anthelmintic (Tacium-Ladry and DesCôteaux 1998).

This pattern of use is similar to that found by market research reports on anthelmintic use in the United States. Independent surveys have shown that about half of all cattle receive no anthelmintic treatment (Forbes 1993). Of the remaining 50%, just over half were treated with ivermectin. More than half (58%) of ivermectin doses were given to young cattle just prior to entering the feedlot, 30% were given to young animals of other types (stockers, weaners or replacements) and the remaining 12% of doses were given to adults. The average number of anthelmintic treatments given to cattle per year in the United States is 1 to 1.3, with younger animals receiving somewhat more frequent treatments (Forbes 1993).

3.1.3 Pigs

The number of pigs raised in Quebec has increased steadily for the past two decades, increasing 35.3% between 1981 and 2001. At the same time, the number of farms has been decreasing, with small farms (less than 1000 heads) suffering the greatest decrease (MAPAQ 2001). At present, Quebec has the highest concentration of large hog farms in Canada. In 2002, the total number of pigs raised in Quebec was 4 280 200, the majority of which were adult fattening and finishing pigs (Appendix 1B). The principal pork producing areas of Quebec are the

same as those for cattle: Chaudières-Appalaches, Montérégie and Centre-du-Québec. These three regions account for 77% of the total herd (BAPE 2003). Pork operations in Montérégie-Ouest have the highest number of pigs per farm, with 1998 pigs per farm (BAPE 2003), but the Chaudières-Appalaches has the highest density of pigs per tillable hectare (1.43 animal units per hectare; BAPE 2003).

In Quebec, pigs do not generally graze on pastures, but are instead kept in various types of high-density housing facilities. Pigs spend most of their life in some type of indoor confinement facility. When pigs are born, they remain with their mothers for approximately 20 days before they are weaned. After weaning, pigs stay in a nursery until they reach 20 to 25 kg, at which point they are transferred to new confinements until they reach market weight (107 kg), which takes about 180 days.

In 2001, Quebec pigs produced approximately 6 565 350 m^3 of raw manure (feces and urine only). The vast majority of pig waste is managed as liquid manure or slurry (98.2%) (BAPE 2003). Approximately three-quarters of this volume is held in open tanks, with most storage facilities being able to hold up to 300 days of slurry production (Statistics Canada 2003). While storage tanks are supposed to be watertight, they are legally allowed to leak at a rate of up to 0.09 cm·per day. This means that at the maximum allowable rate, a 1.2-ha lagoon could legally leak more than 3 million litres per year (Weida 2000). In Quebec, the majority (88–98%) of manure storage facilities (regardless of storage type or livestock) are located more than 30 m away from any type of water source (well, river, stream, wetland, lake, etc).

Nematodes, especially species of *Ascaris, Metastrongylus, Stephanurus* and *Strongyloides*, are important endoparasites of pigs. *Ascaris* is the most widespread genus, causing extensive economic losses due to morbidity, mortality and impaired liver function. The mange mite and swine louse are both considered major ectoparasites of pigs. The extent of parasite problems in herds is currently not known, as no studies have been produced to monitor levels of infection. However, a Danish study found that high rates of transmission can occur inside housing facilities for pigs, but sources of infection vary from one farm to another, depending on management practices (Roepstorff et al. 2001). Therefore, despite living indoors, Quebec pigs remain at risk from parasitic infection.

Although there are no published studies on the use of ivermectin for pigs in Quebec, a survey conducted in Saskatchewan indicated that sows and weanlings are the most commonly treated groups in herds. Approximately three-quarters of respondents used anthelmintics and most followed a planned treatment program. An injectable macrolide was the most commonly administered anthelmintic (use ranged from 33 to 70% among age groups; Wagner and Polley 1997). This may be an underestimation because it does not include ivermectin that is administered to pigs to treat mange. Studies on parasitic infections in pigs in other countries show similar patterns, with ivermectin being the anthelmintic most commonly administered to gilts, boars and sows (Belœil et al. 2003). The manufacturer of ivermectin for pigs recommends that pork producers follow a specific program (the "Herd Mange/Lice Elimination" program, also known as HM/LE) that requires producers to give two doses of ivermectin 18 to 21 days apart to all animals in the herd. After the two-dose treatment, only new additions to the herd would have to be treated.

3.1.4 Sheep

In 2001, there were 225 200 sheep in Quebec, the majority of which were in the Bas-Saint-Laurent region (Appendix 1C). Nematodes are the endoparasites that cause the most severe economic losses in sheep. On a worldwide basis, the heaviest losses in the sheep industry are caused by intestinal roundworms. *Haemonchus* is the dominant genus in warm, wet areas, while *Ostertagia* is especially prevalent in temperate zones. The most widespread external parasite of sheep is the sheep blowfly, which is particularly damaging in Australia and Africa. A study on the health of Quebec's sheep herds indicated that approximately 90% of surveyed farmers treated their herd with an anthelmintic more than once a year — once in the fall, after coming off pasture, and once in the spring, just before sheep were put out to pasture (Bélanger 2001). Most farmers (approximately 82%) used ivermectin for their last anthelmintic treatment. Interestingly, most farmers did not use ivermectin for the next-to-last treatment. Instead, ivermectin was used in rotation with other, non-macrocyclic lactone anthelmintics. Presumably, this is done to prevent resistance problems, which are known to occur in sheep herds (Prichard et al. 2002).

3.1.5 Horses

In 1993, there were 53 476 horses in Quebec (Cochrane 1995). Worldwide, horse parasite control programs are based on regular anthelmintic treatment and not controlled through pasture management (Forbes 1993). Although horse owners make use of strategic treatment programs, it is more common among them to employ tactical programs in which all horses are treated with ivermectin and then fecal counts are used to monitor parasite egg numbers. When counts reach a pre-determined level, horses are treated again. Ivermectin is generally administered at a minimum of two-month intervals (Forbes 1993). The makers of Eqvalan™, the brand name of ivermectin for horses, recommend that all horses in a herd be treated within a regular treatment program and that treatment should begin at 6 to 8 weeks of age.

3.1.6 Aquaculture

Freshwater aquaculture production in Quebec increased steadily until 2000, but has since declined by about 25% (MAPAQ 2003). In the saltwater aquaculture industry, avermectins have been used to control ectoparasitic outbreaks of sea lice (parasitic copepods). Ivermectin was initially used "off-label" to treat sea lice infestations. Concerns about its toxicity to target and non-target organisms led to the development of a less toxic analog, emamectin benzoate (also known as SLICE). Although it is expected that emamectin benzoate will be approved for use in the Canadian aquaculture industry, its use is still administered by the Veterinary Drug Directorate (VDD) through the veterinary emergency release program, which allows veterinarians to prescribe drugs for uses other than their label recommendations. Across Canada, there were 170 emergency veterinary releases for emamectin benzoate in 2002, which accounted for the treatment of 71 509 metric tons of fish with a total of 25.03 kg active ingredient (VDD 2003). However, avermectins are not generally used to treat parasitic infections of fish in Quebec (Uhland 2001). In 2001–2002, there was only one emergency veterinary release for the use of emamectin benzoate for an aquaculture facility in Quebec and none in 2002–2003 (Uhland 2003). The recommended treatment regime for emamectin benzoate is 50 μg/kg body weight (bw) for seven days as an in-feed medication.

Schering-Plough Animal Health, the makers of emamectin benzoate, are attempting to develop a preventative treatment regime that includes treating salmon smolts while they are in

their freshwater holding tanks prior to transferring them to the marine pens. It is unclear whether this practice will potentially have any ramifications for freshwater systems, as there were no indications of what would be done with waste that accumulates in the tanks or with the water from treatment tanks.

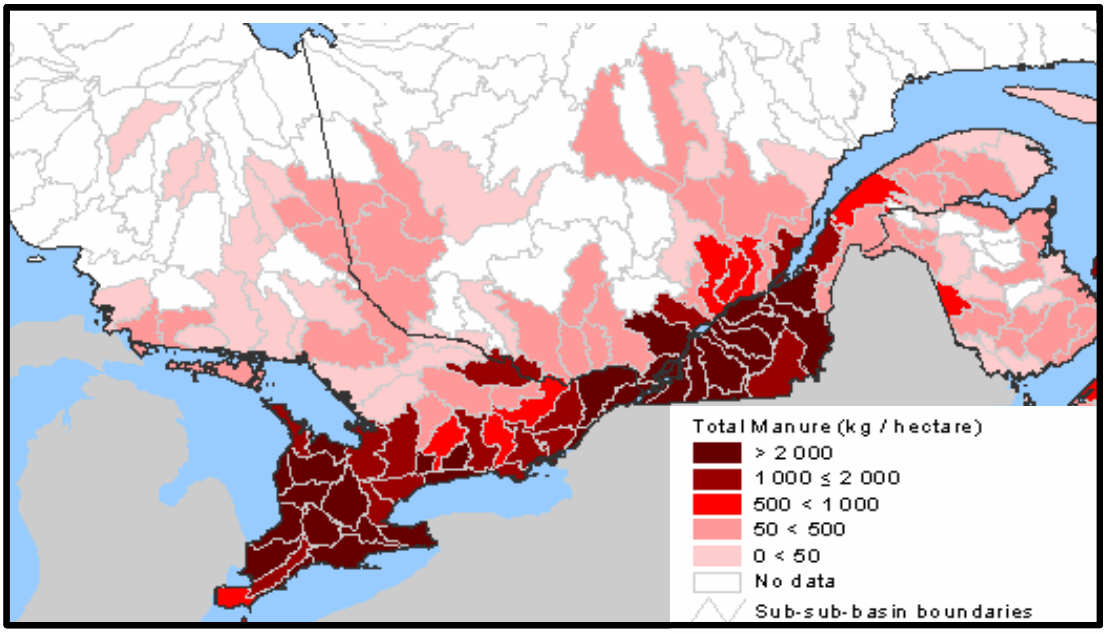
3.1.7 Domestic pets

Very little information has been published on the degree of use of anthelmintics in pets in Quebec. However, a survey conducted by Université de Montréal's Faculty of Veterinary Medicine indicated that of the 92 500 dogs tested for parasitic infections in 1998, only 68 of them tested positive. Roughly half of the dogs that tested positive were from Montreal and its surrounding suburbs (UMFV 1999). According to this survey, 70% of owners had given Heartguard, an ivermectin-based treatment, to their dogs. As for cats, parasitic infections requiring treatment with anthelmintics are apparently rare (UMFV 1999). No information was given for other household pets in this study. The environmental fate of avermectins used in this context will be difficult to estimate, as feces from domestic pets are not intensively managed in the same way as livestock manure. When dogs in suburban areas, especially areas adjacent to lakes, rivers or streams, are treated with heartworm medication, there is a possibility that avermectins will enter those aquatic systems through feces. However, this risk seems minimal relative to the risks in rural settings.

In summary, the agriculture sector in Quebec will likely account for the largest pool of avermectins entering the environment. Although few studies have been done on the use of avermectins in Quebec, the rate of parasitism in some livestock herds and the economic benefits of anthelmintic control indicate that their use is probably widespread and regular. Furthermore, differences in manure management practices among livestock types will play a role in the dispersal of avermectin-treated dung into the environment.

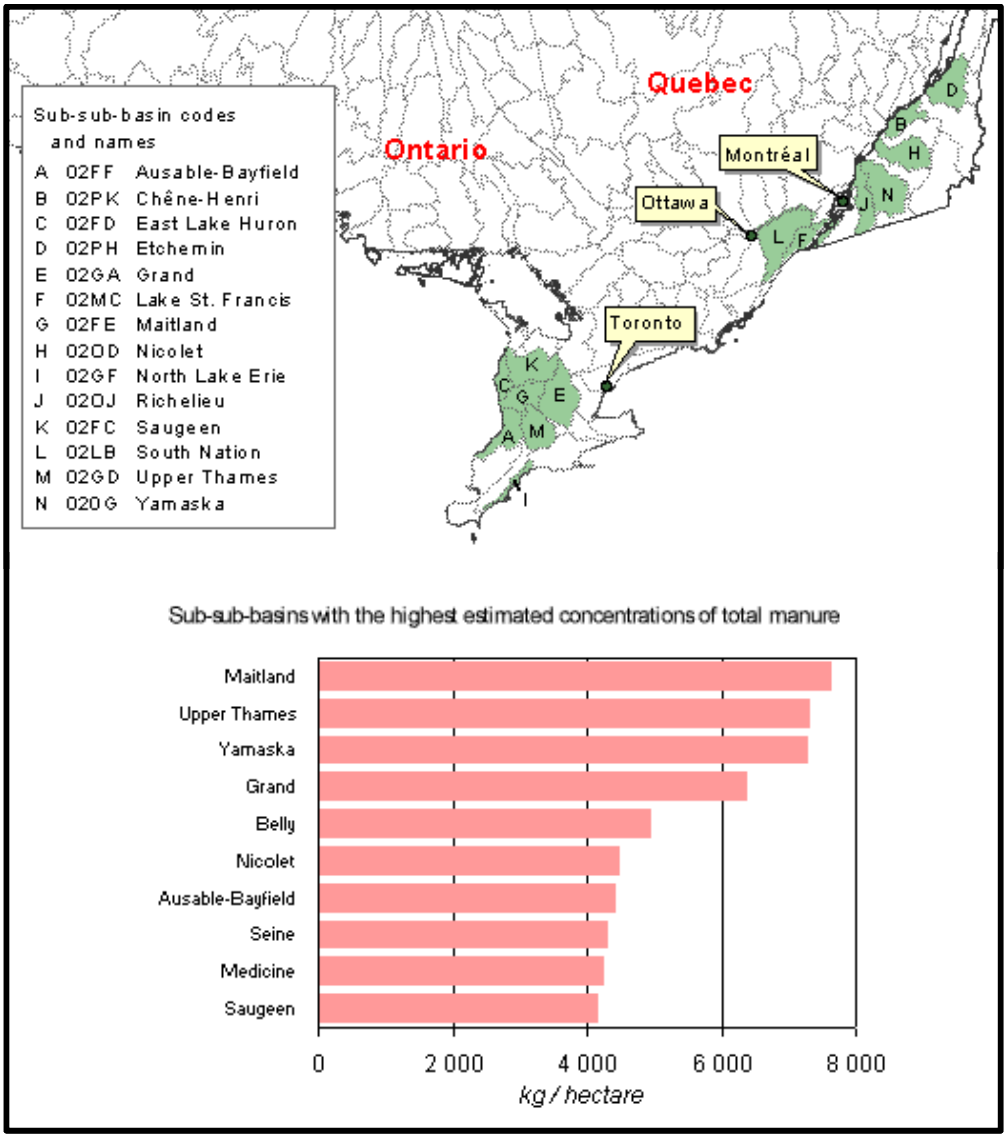
4 Avermectin Use in Quebec

In Quebec, there have been no studies done or databases established to track the use and fate of any veterinary medicines used in livestock management. In the absence of such information, determining the degree of use of avermectins remains somewhat speculative. However, it is reasonable to assume that wherever there is the most livestock, and hence the greatest amount of manure production, there will be a greater probability of avermectins entering the environment and potentially reaching water bodies. We can therefore expect that in regions of southern Quebec, where the density of manure production is highest (Figure 1), particularly in the Yamaska and Nicolet watersheds (Figure 2), there will be more avermectins entering the environment. This probability will be mitigated by adherence to good manure management practices. It is possible, however, that small farms in areas of low animal density will pose a greater risk because there are fewer regulations, less stringent enforcement, and farmers have less money to spend on manure management.



Source: Reproduced from Nancy Hofmann and Laura Kemp (2001). *A Geographic Profile of Manure Production in Canada.* Statistics Canada, Catalogue No. 16F0025XIB.

Figure 1 Total manure production by sub-sub basin in Quebec and Ontario



Source: Reproduced from Nancy Hofmann and Laura Kemp (2001). *A Geographic Profile of Manure Production in Canada.* Statistics Canada, Catalogue No. 16F0025XIB.

Figure 2 Sub-sub basins where manure production exceeds 4000 kg/ha

We can use our knowledge of herd production characteristics by livestock type, combined with recommended and known anthelmintic treatment programs, to estimate the quantity of avermectins entering the environment in a given region in Quebec. In the first model,

the treatment regime was assumed to consist of one subcutaneous injection of 0.2 mg/kg bw per year for cattle; one injection of 0.3 mg/kg bw per year for pigs; and one drench of 0.5 mg/kg bw per year for sheep. The second model includes some of the label recommendations for treatment (all pigs are treated twice, young cattle are treated twice, adult cattle are treated once, and all sheep are treated once) and assumes that the entire herd is treated. It can therefore be seen as a worst-case scenario. Model 3 uses the results from some of the published surveys on use patterns and incorporates these values on the proportion of the herd that is treated, in addition to the label recommendations for frequency of treatment. Regardless of model assumptions, it is clear that there will be a large variation in the total amount of ivermectin being released to the environment. The models are useful, however, for highlighting which livestock is contributing the most ivermectin in a particular region. For example, in the Bas-Saint-Laurent or Abitibi-Témiscamingue region, cattle contribute more ivermectin than do pigs or sheep. In contrast, in the Montérégie region, pigs contribute considerably more ivermectin than do cattle or sheep. This is an important consideration in long-term risk assessment because the actual risk to aquatic environments will be mitigated by manure management and other farming practices. These factors change according to the dominant livestock type in a region.

Models 2 and 3 both assume that at least part of any given herd will be treated more than once per year. The inclusion of different treatment protocols points up the fact that persistence in the environment will also be dependent on livestock type. For example, if we assume that all pigs in a herd are being treated according to the manufacturer's (Merial) Herd Mange/Lice Elimination regime (HM/LE), then every pig will receive two injections in the spring, 21 days apart. That represents over 40 days during which ivermectin will be entering the environment. Therefore, even though Model 1 predicts that the total amount of ivermectin originating from pigs is the same as in Model 3, the environmental risk is different. Furthermore, a region dominated by pigs following the HM/LE protocol would likely have a peak of ivermectin excretion in the spring, when pigs and cows are being treated, with a smaller spike in the fall, when only cows are being treated. In contrast, a region that is dominated by cattle, like the Bas-Saint-Laurent, would have approximately equal peaks in the spring and fall (tables 8, 9 and 10).

Table 8
Estimated total amount of ivermectin administered to Quebec livestock in a typical year – Model 1

Region	Estimated quantity of ivermectin by livestock type (kg)*			Total quantity of ivermectin (kg)
	Pigs	Cattle	Sheep	
Bas-Saint-Laurent	5.28	13.49	1.64	20.41
Saguenay–Lac-Saint-Jean, Côte-Nord	0.34	7.24	0.35	7.94
Quebec City	2.48	4.45	0.08	7.02
Mauricie	4.67	6.58	0.11	11.37
Eastern Townships	7.82	15.48	0.54	23.84
Montreal, Laval, Laurentians	0.86	4.55	0.12	5.53
Outaouais	0.20	6.52	0.17	6.88
Abitibi-Temiscamingue, Nord-du-Québec	0.34	6.20	0.43	6.98
Gaspésie–Îles-de-la-Madeleine	0.00	1.15	0.19	1.34
Chaudière-Appalaches	38.46	26.86	0.36	65.67
Lanaudière	8.61	5.01	0.17	13.79
Montérégie	41.79	26.48	0.54	68.80
Centre-du-Québec	14.82	21.42	0.43	36.68
TOTAL (all regions)				276.24

* All livestock treated once at label-recommended doses.

Note: See Appendix 3A for more details.

Table 9
Estimated total amount of ivermectin administered to Quebec livestock in a typical year – Model 2

Region	Estimated quantity of ivermectin by livestock type (kg)*			Total quantity of ivermectin (kg)
	Pigs	Cattle	Sheep	
Bas-Saint-Laurent	10.57	11.28	1.64	23.48
Saguenay–Lac-Saint-Jean, Côte-Nord	0.68	5.81	0.35	6.84
Quebec City	4.97	3.62	0.08	8.67
Mauricie	9.35	5.64	0.11	15.10
Eastern Townships	15.64	12.79	0.54	28.96
Montreal, Laval, Laurentians	1.73	3.62	0.12	5.47
Outaouais	0.40	5.11	0.17	5.68
Abitibi-Temiscamingue, Nord-du-Québec	0.69	5.07	0.43	6.19
Gaspésie–Îles-de-la-Madeleine		0.9	0.19	1.09
Chaudière-Appalaches	76.92	22.25	0.36	99.52
Lanaudière	17.22	4.09	0.17	21.47
Montérégie	83.57	22.7	0.54	106.80
Centre-du-Québec	29.65	18.24	0.43	48.31
TOTAL (all regions)				377.60

* All pigs twice a year (kg); young cattle twice a year (kg), adult cattle once a year (kg); sheep a drench once a year (kg).

Note: See Appendix 3B for more details.

Table 10
Estimated total quantity of ivermectin administered to Quebec livestock in a typical year – Model 3

Region	Estimated quantity of ivermectin by livestock type (kg)*			Total quantity of ivermectin (kg)
	Pigs	Cattle	Sheep	
Bas-Saint-Laurent	5.32	7.40	0.29	13.01
Saguenay–Lac-Saint-Jean, Côte-Nord	0.34	3.79	0.06	4.20
Quebec City	2.50	2.37	0.01	4.89
Mauricie	4.71	3.71	0.02	8.44
Eastern Townships	7.88	8.38	0.10	16.36
Montreal, Laval, Laurentians	0.87	2.37	0.02	3.26
Outaouais	0.20	3.33	0.03	3.56
Abitibi-Temiscamingue, Nord-du-Québec	0.35	3.32	0.08	3.74
Gaspésie–Îles-de-la-Madeleine		0.59	0.03	0.62
Chaudière-Appalaches	38.74	14.59	0.06	53.39
Lanaudière	8.67	2.68	0.03	11.38
Montérégie	42.10	14.93	0.10	57.12
Centre-du-Québec	14.93	11.99	0.08	27.00
TOTAL (all regions)				206.98

* 50% of pigs twice a year; 67% of young cattle twice a year; adult cattle once a year; 82% of sheep a drench once a year.

Note: See Appendix 3C for more details.

5 Discussion

5.1 SOURCES OF CONTAMINATION

Agriculture, particularly intensive farming, has been linked to the environmental degradation of freshwater systems in Quebec (Patoine and Simoneau 2002). Despite the pervasive use of medicines in livestock, very little is known about the environmental risk of these drugs in freshwater systems. Agricultural scientists have generally concluded that the use of ivermectin in current farming practices poses little or no threat to freshwater ecosystems. While it is true that the physical/chemical properties of ivermectin will likely preclude it from accumulating in the water column of receiving waters (Halley et al. 1989a, Nessel et al. 1989, Wislocki 1989), its high binding affinity for soils and other organic matter might result in its accumulation in the sediments of lakes and rivers. This environmental compartment seems to have been ignored by environmental assessments up to this point. There are four possible routes that avermectins may take in moving from livestock to freshwater: groundwater, runoff, soil erosion, and direct deposition.

5.1.1 Groundwater and runoff

Laboratory and field experiments have demonstrated that ivermectin residues bind tightly to soil (Nessel et al. 1989, Halley et al. 1989a). Compounds possessing $K_{oc} > 1000$ are considered tightly bound to organic matter in soil and immobile in the environment. Ivermectin has a K_{oc} of 12 600 and 15 700, depending on soil type, and is therefore classified as immobile. Nessel et al. (1989) collected runoff from an experimental feedlot and found that when cattle were stocked at a density of 0.05 cows/m^2 (5 cows/1000 ft^2) and injected with one dose of ivermectin (0.3 µg ivermectin/kg cow), the concentration of ivermectin in surface and subsurface runoff water was less than 2 and 4.6 ppt, respectively, concentrations the authors considered negligible. When cultures of *D. magna* were exposed to the runoff, toxic thresholds exceeded the maximum exposure concentration (200% of initial runoff water by volume). The authors concluded that the runoff was not toxic. The animal stocking density used in this experiment reflects the lower end of densities in Quebec as 75% of all livestock are maintained at densities of 0.04–0.24 a.u. /m^2 (Beaulieu 2001).

To test for impacts on groundwater, Halley et al. (1989a) performed a variety of tests using leaching columns. To measure the concentration of ivermectin that moved vertically through soil, Halley et al. (1989a) mixed feces from a steer dosed with radiolabelled ivermectin with soil and added this mixture to a variety of soil types. Water was percolated through the column and collected for 38 days. Recovery of radiolabel ranged from 10% to 48%, depending on soil type. However, there was no detectable ivermectin in the eluate: all the radioactivity was composed of metabolites of ivermectin. Further analysis showed that 39–45% of the radioactivity remained in the top 5 cm of the soil column for each soil type and analysis of the eluate showed that the radioactivity was due mainly to the metabolites of ivermectin and not the parent compound. In a similar series of column leaching experiments, eluate from mixtures of soil and dosed or spiked samples of feces showed little (100% toxic at 6.5 ppb) or no toxicity to *Daphnia magna.* These results are not surprising given the high binding affinity for organic matter and the low solubility of ivermectin in water. It therefore seems reasonable to conclude that neither runoff nor groundwater will be a significant source of ivermectin toxicity to freshwater ecosystems.

5.1.2 Soil erosion

If manure from treated animals is mixed with agricultural soil as fertilizer, then it is possible that erosional processes could move ivermectin bound to soil particles from fields into adjacent receiving waters. Although erosion is not the most widespread soil degradation problem for Quebec agricultural lands, it can be significant in local areas, particularly those that are dominated by monocultures of crops like corn (Tabi et al. 1990). Ten percent of agricultural land dominated by monoculture has soil degradation problems due to water erosion and 6% due to wind erosion (Tabi et al. 1990). In the Bois-Francs, Richelieu–Saint-Hyacinthe, southwest Montreal, and north of Montreal regions, a high proportion of the land is given over to monocultures (26–55%), which puts these regions at higher risk for soil erosion (Tabi et al. 1990). In the Boyer River watershed, 1 to 11 tonnes of soil per hectare is lost each year due to erosional processes. Halley et al. (1989b) estimated the predicted environmental concentration (PEC) of ivermectin in the soil of agricultural fields using ivermectin-treated manure as fertilizer. To calculate the PEC, the authors assumed there was no degradation of ivermectin after

excretion, that all ivermectin was present as parent compound and that all manure had the same concentration. They concluded that the concentration of ivermectin in fields would be 0.04–0.2 ppb (waste from water-washed swine and feedlot cattle or swine, respectively).

Using the 0.2 ppb as a worst-case scenario, we can estimate that given the aforementioned rate of soil erosion, 200 to 2200 mg of ivermectin per hectare could be entering waterways in this watershed. The soil lost due to erosion accounts for 78% of the suspended sediments found in adjacent bodies of water in the Boyer watershed (MENV 2003a).

The risk of soil translocation due to erosion will be highest when crop coverage is lowest, i.e. in the fall after harvesting. This risk can be diminished if farmers leave above-ground crop residues after harvesting. However, most farmers in Quebec do not adhere to this soil conservation practice; in 2001, only 18.5% of the total farmed area had crop residues after harvest (MENV 2003a). The post-harvest period of higher erosion risk coincides with the period of time when a large proportion of animals would be treated with ivermectin, and marks the end of the period during which farmers are allowed to spread manure as fertilizer. The toxicity of the sediment-bound ivermectin will be mitigated by the length of time it spends on the field, where it will be subject to aerobic metabolism and photodegradation, the amount of time the manure had been stored prior to its application, and how much untreated manure it was mixed with.

5.1.3 Direct deposition

The direct deposition of ivermectin-treated feces represents the greatest threat to aquatic ecosystems. It occurs in potentially two ways: 1) livestock having access to rivers, streams and ponds because of poor riparian management, or 2) spreading of ivermectin-treated manure as fertilizer near watercourses.

Riparian management tends to be poor in agricultural areas. Farmers remove vegetation right up to the edge of a stream or waterbody, allowing access to livestock. For example, only 30% of riparian areas in the Chaudière River are classified as being in excellent or good condition (MENV 2003b). In the Etchemin River, 40% of the riparian areas along the main branch have lost their “natural aspect” (CBE 2004). The loss of riparian areas is partially due to the conversion of riparian vegetation to monocultural farming to allow farmers to spread more manure (manure can only be spread as fertilizer on lands under cultivation).

Although environmental assessments of ivermectin-based products modelled direct inputs of ivermectin into ponds and rivers, the assessments only considered what the final concentration would be in the water column, and not the concentration in sediments. We can, however, take a scenario similar to that described in the environmental assessment for ivermectin to be administered to cattle (adult cows in a one-acre pond; FDAH 1997), and add some estimates of what the concentrations in sediments might be as a result of livestock defecating directly into a body of water.

Consider a pond with an area of 0.4 hectares (1 acre), a mean depth of 1.2 m and a volume of 4.9×10^6 L of water (FDAH 1997). The total daily manure output of one adult dairy cow is approximately 67 kg and generally an adult cow will defecate about ten times per day (Marsh and Campling 1970). For a herd with 50 cows grazing on a field[6], we assume that 10% of those cows per day are going to enter the pond and defecate once, which would result in 33.5 kg of manure being deposited in the pond. As a worst-case scenario, each of these cows would have been treated with ivermectin at a dosage of 0.2 mg/kg bw and 60% of the dosage would be excreted in the first three days (Montforts et al. 1999). If the ivermectin is excreted equally over three days, then each day the cows would be excreting approximately 127 mg ivermectin. As we are assuming that only 10% of the daily fecal output will reach the pond, then 12.7 mg of ivermectin will enter the pond at a concentration of 0.38 ppm (12.7 mg ÷ 33.5 kg manure). This concentration lies between the maximum concentrations measured by Lumaret et al. (1993) and Sommer and Stefansson (1993) for adult dairy cattle treated with a subcutaneous injection (Table 3). This concentration of ivermectin is higher than sediment concentrations that are toxic to *D. magna* (0.039 ppm via sediment) and *Corophium volutator* (0.18 ppm via sediment), but lower than the toxic thresholds for *Crangon septemspinosa* (8.5 to 13.1 ppm via sediment) (Table 7). However, if we assume that all the feces become incorporated into the top 5 cm of sediment in the pond (Cannavan et al. 2000), then we could expect the concentration to decrease by approximately one order of magnitude to 0.042 ppb (see Appendix 4 for calculations). This concentration would be below all the measured toxic thresholds to date. The concentration of

[6] From Caldwell et al. (1998), survey showed that 63% of Quebec dairy herds have 30–49 cows in the herd.

ivermectin in the benthic environment would obviously be altered by differences in flow, temperature, time of the year, and size of the waterbody.

Avermectins may also be directly deposited into aquatic ecosystems through the spreading of manure for fertilizer. Farm census data from 2000 indicates that in Quebec, most farmland receives manure inputs from a solid spreader (52.5%) or surface liquid spreader (42%) (Statistics Canada 2001). Only 4% of these lands receive inputs through liquid injection, which incorporates the manure directly into the soil. The surface application of manure without plough-down or disking poses the greatest risk of runoff. Currently, spreading of manure is only allowed between April 1 and October 1. As of April 2005, slurry has to be applied with a low slope (*rampe basse*) machine; use of spreading machines that project the manure more than 25 m is prohibited; and spreading is not allowed in riparian areas (defined by municipalities — where there is no municipal definition of riparian area, then spreading is prohibited within 3 m of rivers and 1 m from drainage ditches) (MENV 2003a). It is difficult, however, to assess the potential risk of avermectins collecting in freshwater systems through this route. First, many farms have long-term storage capacity for manure (on average, Quebec farms can store 282 days worth of slurry production). Avermectin-contaminated manure will be diluted with avermectin-free manure, thus diminishing the concentration in the storage facility. Furthermore, farmers tend to fully homogenize the manure before they use any of it for spreading. Conversely, a significant proportion of farms in Quebec have inadequate storage facilities for manure or none at all. As of 2001, 5200 farms did not have adequate storage systems for manure (MENV 2003a). Most of these farms were generally smaller beef and dairy farms and several were situated outside of the high-density farming areas. In addition, 5700 farms were small enough (less than 35 animal units) to qualify for exemptions to the manure management regulations. The current manure management regulations apply only to farms with at least 40 animal units.

Initial studies done on the persistence of ivermectin in terrestrial soils indicated that once bound to soil, ivermectin could persist for 7–14 days under typical summer conditions and 91 to 217 days under typical winter conditions. Field studies of emamectin benzoate show that half-lives in marine sediments can reach up to 164–175 days (SPAH 2002), indicating that avermectins could potentially exert lethal and sublethal impacts for a considerable period of time. This suggests that, over the course of a grazing season, even if direct inputs to freshwater systems

are erratic, there could be sustained toxic impacts at a local scale (i.e. within several metres of wherever deposition occurred).

5.2 SPECIES OF CONCERN IN FRESHWATER ECOSYSTEMS

It is clear from the preceding discussion that avermectins can have lethal and sublethal effects on a wide range of organisms. It is difficult to narrow down which freshwater taxa would be most susceptible in light of the paucity of experimental data for freshwater organisms and the variability in species sensitivity across taxa. However, it stands to reason that, given the high binding affinity of avermectins to organic material and their mode of action, benthic invertebrates would be the most susceptible to exposure in freshwater environments. Data gathered from terrestrial studies and aquaculture studies can help identify which taxa might be at risk in freshwater environments.

In agricultural pastureland ecosystems, one infraorder and one suborder of Diptera (Cyclorrhapha and Nematocera, respectively) are considered the most sensitive to exposure. Both of these taxonomic groups have representatives in freshwater systems. Within the Cyclorrhapha, there are six families that have freshwater life stages, namely, Ephydridae, Syrphidae, Muscidae, Phoridae, Scathophagidae and Sciomyzidae. The Nematocera have the greatest number of aquatic representatives, with 13 out of 23 nematoceran families being aquatic (Peckarsky et al. 1990). These include some of the most important dipteran families (in terms of biomass, productivity or as important prey items for higher trophic levels) for aquatic systems, including Ceratopogonidae, Chaoboridae, Chironomidae, Culicidae and Dixidae (Peckarsky et al. 1990).

To date, only a few studies have specifically examined avermectin exposure to freshwater invertebrates (aside from the initial toxicity bioassays done on *D. magna*). Ali et al. (1997) exposed invertebrates in artificial ponds to various concentrations of abamectin, which was applied as a spray to the pond to mimic its most likely route of entry – crop spraying for pests. The study found that larval chironomid abundances (*Chironomus* spp*., Goeldichironomus holoprasinus, Polypedlum* spp. and *Tanytarsus* spp.) decreased significantly (94–99%) seven days after exposure to concentrations ranging from 3.13 ppb to 50.0 ppb. Ephemeropteran, hemipteran and coleopteran nymphs also showed significant reductions, but not as dramatic as those of the chironomids. Ding et al. (2001) showed that when freshwater oligochaetes were

exposed to dissolved abamectin, they exhibited a variety of sublethal effects at concentrations of 300 nmol, including reduced swimming. Furthermore, marine benthic invertebrates like polychaetes, mysids and gammarid amphipods are particularly sensitive to a range of doses of ivermectin (Table 5). Combined, the studies of freshwater and marine systems indicate that future research on the impacts of exposure to avermectins in fresh water should focus on those invertebrates that live in close association with the top layers of sediments, particularly nematoceran dipterans, ephemeropterans, coleopterans, as well as amphipods and oligochaetes.

Waddy et al. (2002) have demonstrated that emamectin benzoate can disrupt the endocrine systems of the American lobster (*H. americanus*). These authors observed that moulting was induced in response to exposure and suggested that this might be a result of emamectin benzoate interfering with the function of the moult-inhibiting hormone. Lobsters and crayfish are both decapod crustaceans and have similar physiologies (Brusca and Brusca 1990). In decapod crustaceans, the moult-inhibiting hormone (MIH) is presumed to regulate moulting by inhibiting the secretion of ecdysteroids from Y-organs (Dell et al. 1999). MIHs have been found in a variety of crustaceans, including freshwater crustaceans like the crayfish (Dell et al. 1999). The abundances of native crayfish populations have been decreasing in recent years as a result of competition from non-native crayfish and habitat loss (Taylor et al. 1996). Taylor et al. (1996) estimated that approximately 50% of all crayfish species in the U.S. and Canada are imperilled to different degrees and require some form of conservation recognition. Therefore, understanding new threats to this taxonomic group would be of considerable conservation importance for Canadian biodiversity.

Although avermectins do not seem to bioaccumulate in fish (Van den Heuvel et al. 1996), they can be toxic (Table 2) and can pass the blood/brain barrier (Høy et al. 1990). So far, only fish that are of interest to the aquaculture industry have been studied extensively. This has resulted in a bias towards studying fish that are associated with the water column. Furthermore, most exposure has been performed in the dissolved phase, which might underestimate the threat posed to fish that live in close association with sediments. For example, although carp are a benthic fish species, exposure to abamectin was applied in the dissolved phase (Wislocki et al. 1989).

Finally, much recent attention has been paid to the global decline of amphibians and reptiles. Pesticide use in agricultural areas (Gibbons et al. 2000) is one of the mechanisms used to explain the observed declines. Although it seems that ivermectin is safe for snakes when administered at doses similar to those given to livestock, it is not considered safe for adult turtles (Little et al. 2002). Apparently, as in salmon, the therapeutic index for turtles is very narrow and can result in death for the target animal. To date, there is no information available for life stages other than the adult stage in reptiles and amphibians — despite the fact that young life stages of amphibians are particularly sensitive to exposure to toxicants.

It is clear that avermectins can exert severe lethal and sublethal impacts on non-target organisms at multiple trophic levels. The high potency against terrestrial invertebrates raises significant concerns about how freshwater benthic communities will be impacted by exposure to avermectins. By potentially reducing the diversity (McCracken and Foster 1993) and abundance of some size classes (Collier and Pinn 1998) of benthic invertebrates available to other trophic levels, avermectins may disrupt the efficiency of energy transfer in aquatic ecosystems. In addition, research indicates that, unlike most vertebrates, avermectins can accumulate in the brains of fish and some fish species have a very low tolerance to exposure. Therefore, exposure to avermectins can affect aquatic ecosystems by two different means: direct losses of biodiversity (i.e. species loss) and decreases in ecosystem function (decreased efficiency of energy transfer).

The general conclusion of agricultural scientists that the use of avermectins does not pose a threat to freshwater pelagic organisms is relatively reasonable. However, the underlying assumption is that all farmers who use avermectins also maintain good farming practices — maintenance of intact riparian buffers, exclusion of cattle from waterways, employing soil conservation techniques to reduce erosion, and adherence to the guidelines for storage and spreading of manure. In an ideal world, where all farmers maintained ideal conservation farming practices, there would be a very low risk of exposure to any freshwater organism. In reality, it is not unreasonable to expect that avermectins could be entering freshwater systems at concentrations high enough to exert negative effects. It is currently difficult to develop a thorough risk assessment for freshwater systems because there is a lack of concrete data on the rate of avermectin use in Quebec, an absence of data/measurements of avermectins in the sediments of freshwater ecosystems in agricultural areas, and limited toxicological information

on the impacts of avermectins on freshwater organisms. The results of this review indicate that the risk posed by the use of avermectins in Quebec warrants more research, through laboratory studies and field studies, to fully characterize the environmental risk of their use and aid in developing appropriate management plans.

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Appendices

Appendix 1 Size of livestock herd in Quebec, by region

A Number of cattle (000s of heads) in 2002

Administrative region	Total	Steers	Veal	Dairy heifer	Dairy cow	Beef heifer	Bull	Beef cow
Bas-Saint-Laurent	113.6	1	30.2	20.5	40	4.4	1.1	16.4
Saguenay–Lac-Saint-Jean, Côte-Nord	58.3	0.2	15.5	7.8	23.8	2	0.5	8.6
Quebec City	38.7	1.8	10.9	4.5	13.3	1.5	0.4	6.3
Mauricie	63.5	13.6	13.5	8.5	19.8	1.5	0.5	6.1
Eastern Townships	133.5	4.4	32.6	19.6	40.2	7.1	1.8	27.8
Montreal, Laval, Laurentians	42	7.3	9.1	1.9	13	2.1	0.4	8.2
Outaouais	59.6	1.6	11.5	2.5	5.4	7.3	1.4	29.9
Abitibi-Témiscamingue, Nord-du-Québec	60.4	2	17.2	3.7	8.8	6.1	0.8	21.8
Gaspésie–Îles-de-la-Madeleine	10.6	0.1	2.6	0.4	1.3	1.1	0.2	4.9
Chaudière-Appalaches	235.8	14.9	60.7	33.3	75.8	9	2.9	39.1
Lanaudière	44.7	6.5	10.2	4.4	16.2	1.6	0.4	5.4
Montérégie	252.1	23	82.9	34.7	82.7	6.6	2.6	19.7
Centre-du-Québec	197.2	5.6	67.1	30.2	62.7	6.2	1.5	23.8
Total	1310	82	364	172	403	56.5	14.5	218

Source: ISQ, 2002a.

B Number of pigs (000s of heads) in 2002

Administrative region	Breeding pigs	All other pigs
Bas-Saint-Laurent, Gaspésie–Îles-de-la-Madeleine	25.7	147.1
Saguenay–Lac-Saint-Jean, Côte-Nord	1.3	10.1
Quebec City	9.4	74.2
Mauricie	15.4	144
Eastern Townships	20.9	250.1
Montreal, Laval, Laurentians	2.8	26.7
Outaouais	1	5.5
Abitibi-Témiscamingue, Nord-du-Québec	0.8	11.2
Chaudière-Appalaches	136.5	1166.2
Lanaudière	27	267.8
Montérégie	133.6	1294.9
Centre-du-Québec	46	462
Total	420.4	3859.8

Source: ISQ, 2002b.

C Number of sheep (000s of heads) in 2001

Administrative region	Sheep
Bas-Saint-Laurent	72.1
Saguenay–Lac-Saint-Jean, Côte-Nord	15.6
Quebec City	3.6
Mauricie	4.9
Eastern Townships	23.6
Montreal, Laval, Laurentians	5.2
Outaouais	7.3
Abitibi-Témiscamingue, Nord-du-Québec	18.9
Gaspésie–Îles-de-la-Madeleine	8.4
Chaudière-Appalaches	15.7
Lanaudière	7.3
Montérégie	23.6
Centre-du-Québec	19.0
Total	225.2

Source: ISQ, 2002c.

Appendix 2 Manure production in Quebec, by region

A Manure production of cattle (kilograms per day)

Administrative region	Beef heifer	Beef cow	Veal	Bull	Dairy heifer	Dairy cow	Steers
Bas-Saint-Laurent	51 920	469 040	123 518	57 431	604 955	268 7600	4 090
Saguenay–Lac-Saint-Jean, Côte-Nord	23 600	245 960	63 395	26 105	230 178	1 599 122	818
Quebec City	17 700	180 180	44 581	20 884	132 795	893 627	7 362
Mauricie	17 700	174 460	55 215	26 105	250 835	1 330 362	55 624
Eastern Townships	83 780	795 080	133 334	93 978	578 396	2 701 038	17 996
Montreal, Laval, Laurentians	24 780	234 520	37 219	20 884	56 069	873 470	29 857
Outaouais	86 140	855 140	47 035	73 094	73 775	362 826	6 544
Abitibi-Témiscamingue, Nord-du-Québec	71 980	623 480	70 348	41 768	109 187	591 272	8 180
Gaspésie–Îles-de-la-Madeleine	12 980	140 140	10 634	10 442	11 804	87 347	409
Chaudière-Appalaches	106 200	1 118 260	248 263	151 409	982 683	5 093 002	60 941
Lanaudière	18 880	154 440	41 718	20 884	129 844	1 088 478	26 585
Montérégie	77 880	563 420	339 061	135 746	1 023 997	5 556 613	94 070
Centre-du-Québec	73 160	680 680	274 439	78 315	891 202	4 212 813	22 904
Total (kg/d)	666 700	6 234 800	1 488 760	757 045	5 075 720	27 077 570	335 380
Total (kg/y)	243 345 500	2 275 702 000	543 397 400	276 321 425	1 852 637 800	9 883 313 050	122 413 700
Mean manure production (kg/d/animal)*	11.8	28.6	4.09	52.21	29.5	67.19	4.09

* Values for individual manure production are from the Michigan State Department of Agriculture.

Note: Total manure production in a region was calculated by multiplying the number of heads of cattle by mean individual manure production per day. Information on the number of heads of cattle in a region is drawn from the Institut de la statistique du Québec (2002a).

B Manure production of pigs (kilograms per day)

Administrative region	Total number of pigs (000s)**	Manure production (kg/d)***		
		Breeding pigs	Other pigs	Total
Bas-Saint-Laurent, Gaspésie–Îles-de-la-Madeleine	172.8	262 654.00	449 390.50	712 044.50
Saguenay–Lac-Saint-Jean, Côte-Nord	11.4	13 286.00	30 855.50	44 141.50
Quebec City	83.6	96 068.00	226 681.00	322 749.00
Mauricie	159.4	157 388.00	439 920.00	597 308.00
Eastern Townships	271.0	213 598.00	764 055.50	977 653.50
Montreal, Laval, Laurentians	29.5	28 616.00	81 568.50	110 184.50
Outaouais	6.5	10 220.00	16 802.50	27 022.50
Abitibi-Témiscamingue, Nord-du-Québec	12.0	8 176.00	34 216.00	42 392.00
Chaudière-Appalaches	1 302.7	1 395 030.00	3 562 741.00	4 957 771.00
Lanaudière	294.8	275 940.00	818 129.00	1 094 069.00
Montérégie	1 428.5	1 365 392.00	3 955 919.50	5 321 311.50
Centre-du-Québec	508.0	470 120.00	1 411 410.00	1 881 530.00
Total manure production (kg/day)		4 296 488.00	11 791 689.00	16 088 177.00
Total annual manure production (kg/year)		1 568 218 120	4 303 966 485	5 872 184 605
Mean manure production (kg/d/pig)*		10.2	3.05	

* Values taken from the Michigan State Department of Agriculture. ** Values drawn from the Institut de la statistique du Québec (2002b). *** Total manure production by region = (number of pigs) × (mean daily individual manure production).

C Manure production of sheep (kilograms per day)

Administrative region	Total number of sheep (000s)**	Manure production (kg/day)***
Bas-Saint-Laurent	72.1	131 222.0
Saguenay–Lac-Saint-Jean, Côte-Nord	15.6	28 392.0
Quebec City	3.6	6 552.0
Mauricie	4.9	8 918.0
Eastern Townships	23.6	42 952.0
Montreal, Laval, Laurentians	5.2	9 464.0
Outaouais	7.3	13 286.0
Abitibi-Témiscamingue, Nord-du-Québec	18.9	34 398.0
Gaspésie–Îles-de-la-Madeleine	8.4	15 288.0
Chaudière-Appalaches	15.7	28 574.0
Lanaudière	7.3	13 286.0
Montérégie	23.6	42 952.0
Centre-du-Québec	19.0	34 580.0
Manure production (kg) per day		409 864.0
Manure production (kg) per year		149 600 360.0
Mean manure production (kg/d/sheep)*		1.82

* Values taken from the Michigan State Department of Agriculture. ** Values drawn from the Institut de la statistique du Québec (2002b). *** Total manure production by region = (number of sheep) × (mean daily individual manure production).

Appendix 3 Estimated total amount of ivermectin administered in a typical year to livestock in Quebec

A Estimated total quantity of ivermectin administered to pigs, by region

Administrative region	Number of pigs (000s)	Average weight (kg)*	Model 1** (kg)	Model 2*** (kg)	Model 3† (kg)
Bas-Saint-Laurent, Gaspésie–Îles-de-la-Madeleine	172.8	101.94	5.28	10.57	5.32
Saguenay–Lac-Saint-Jean, Côte-Nord	11.4	99.15	0.34	0.68	0.34
Quebec City	83.6	99.02	2.48	4.97	2.50
Mauricie	159.4	97.75	4.67	9.35	4.71
Eastern Townships	271.0	96.19	7.82	15.64	7.88
Montreal, Laval, Laurentians	29.5	97.62	0.86	1.73	0.87
Outaouais	6.5	102.35	0.20	0.40	0.20
Abitibi-Témiscamingue, Nord-du-Québec	12.0	95.35	0.34	0.69	0.35
Chaudière-Appalaches	1 302.7	98.41	38.46	76.92	38.74
Lanaudière	294.8	97.35	8.61	17.22	8.67
Montérégie	1 428.5	97.51	41.79	83.57	42.10
Centre-du-Québec	508.0	97.27	14.82	29.65	14.93
Total	4 280.2	97.88	125.69	251.37	126.61

* The average weight of pigs is the weighted average as determined by the proportion of breeding pigs (mean weight = 170.25 kg) relative to the other categories of pigs (mean wight = 90.8 kg).

** Model 1: All pigs are treated once a year with one injection of 0.3 mg of ivermectin per kilogram of pig. Therefore, the total quantity of ivermectin in a region = 0.3 × mean weight of pig × number of pigs in the region.

*** Model 2: To rid the herd of parasites, all pigs are treated once a year with an injection of 0.3 mg of ivermectin per kilogram of pig, as with Merial's HM/LE program. Therefore, the total quantity of ivermectin in a region = (2 × 0.3) × mean weight of pig × number of pigs in the region.

† Model 3: 50% of the pig herd is treated with one injection twice a year. These figures are based on estimates made by Wagner and Polley's (1997) survey of Saskatchewan pig farmers. Therefore, the total quantity of ivermectin in a region = (2 × 0.3) × mean weight of pig × (number of pigs in the region/2).

B Estimated total quantity of ivermectin administered to cattle, by region

Administrative region	Number of cattle (000s)	Mean weight* (kg)	Model 1** (kg)	Model 2*** (kg)	Model 3† (kg)
Bas-Saint-Laurent	113.6	395.82	8.99	11.28	7.40
Saguenay–Lac-Saint-Jean, Côte-Nord	58.3	414.07	4.83	5.81	3.79
Quebec City	38.7	383.46	2.97	3.62	2.37
Mauricie	63.5	345.46	4.39	5.64	3.71
Eastern Townships	133.5	386.64	10.32	12.79	8.38
Montreal, Laval, Laurentians	42.0	361.18	3.03	3.62	2.36
Outaouais	59.6	364.48	4.34	5.11	3.33
Abitibi-Témiscamingue, Nord-du-Québec	60.4	342.37	4.14	5.07	3.32
Gaspésie–Îles-de-la-Madeleine	10.6	362.70	0.77	0.90	0.59
Chaudière-Appalaches	235.8	379.66	17.90	22.25	14.59
Lanaudière	44.7	373.90	3.34	4.09	2.68
Montérégie	252.1	350.10	17.65	22.70	14.93

Administrative region	Number of cattle (000s)	Mean weight* (kg)	Model 1** (kg)	Model 2*** (kg)	Model 3† (kg)
Centre-du-Québec	197.2	362.12	14.28	18.24	11.99
Total			96.96	122.11	79.44

* The average weight of cattle is the weighted average as determined by mean weight of cattle type (e.g. mean weight of a beef heifer of 204 kg and mean weight of a beef cow of 454 kg).

** Model 1: All cattle are treated once a year with an injection of 0.2 mg of ivermectin per kilogram of cow. Therefore, the total quantity of ivermectin in a region = 0.2 × mean weight of cows × number of cows in the region.

*** Model 2: All young cows are treated twice a year and all adults treated once a year with an injection of 0.2 mg of ivermectin per kilogram of cow. Therefore, the total quantity of ivermectin in a region = [(2 × 0.2) × mean weight of young cows × number of young cows in the region] + [(1 × 0.2) × mean weight of adult cows × number of adult cows in the region].

† Model 3: 68% of young cows are treated twice a year and 32% of adults treated once a year with an injection of 0.2 mg of ivermectin per kg of cow. These proportions are based on surveys of anthelmintic use in dairy cows in Quebec (Caldwell et al., 2002). Therefore, the total quantity of ivermectin in a region = [(2 × 0.2) × mean weight of young cows × (0.68 × number of young cows in the region)] + [(1 × 0.2) × mean weight of adult cows × (0.32 × number of adult cows in the region].

C Estimated total quantity of ivermectin administered to sheep, by region

Administrative region	Number of sheep	Models 1 and 2* (kg)	Model 3** (kg)
Bas-Saint-Laurent	72 100.00	1.64	0.29
Saguenay–Lac-Saint-Jean, Côte-Nord	15 600.00	0.35	0.06
Quebec City	3 600.00	0.08	0.01
Mauricie	4 900.00	0.11	0.02
Estrie	23 600.00	0.54	0.10
Montreal, Laval, Laurentians	5 200.00	0.12	0.02
Outaouais	7 300.00	0.17	0.03
Abitibi-Témiscamingue, Nord-du-Québec	18 900.00	0.43	0.08
Gaspésie–Îles-de-la-Madeleine	8 400.00	0.19	0.03
Chaudière-Appalaches	15 700.00	0.36	0.06
Lanaudière	7 300.00	0.17	0.03
Montérégie	23 600.00	0.54	0.10
Centre-du-Québec	19 000.00	0.43	0.08
Total		5.11	0.92

* Models 1 and 2: All sheep were treated once a year with an injection of 0.5 mg of ivermectin per kilogram of sheep. Therefore, the total quantity of ivermectin by region = 0.5 × mean weight of sheep × number of sheep in the region.

** Model 3: 82% of sheep are treated once a year with an injection of 0.5 mg of ivermectin per kilogram of sheep. These proportions are based on a survey of sheep health in Quebec (Bélanger et al., 2002). Therefore, the total quantity of ivermectin in a region = (0.5 × mean weight of sheep) × (0.82 × number of sheep in the region).

Note: The mean weight of sheep used was 45.4 kg.

Appendix 4 Estimated amount of ivermectin entering a pond

Parameter/Assumption	Value
Weight of a typical adult dairy cow	635 kg*
Total daily manure production	67.19 kg
Amount of manure produced/excretion	67.19/10** = 6.72 kg
If 5 dairy cows receive 0.2 mg of ivermectin per kilogram of body weight and they void into a pond on the second day after treatment:	5 cows × 6.7 kg = 33.5 kg
• Amount of ivermectin administered to each cow	(0.2 mg Ivm/kg) × 635.6 kg = 127.12 mg Ivm/cow
• Total amount of ivermectin administered to all cows	127.12 mg Ivm per cow × 5 cows = 635.6 mg Ivm
• Amount of ivermectin excreted each day for the first three days post dosing	(635.6 mg Ivm × 60%***)/3 days = 127.12 mg
• Amount of ivermectin in one pat	127.12/10 = 12.712 mg
• Concentration of ivermectin in one pat	12.712/6.72 = 0.38 mg/kg
• Concentration of ivermectin in pond sediment	303 000 kg × 0.38 mg/kg = 0.000 041 95 ppb or 0.042 ppm
Pond dimensions†	
• One-acre pond = 4047 m^2 × depth of 2 m =	8 094 000 L
• Volume of top 5 cm of sediment = 0.05 m × 4047 m^2 =	202 m^3
• Mass = 202 m^3 × 1500 kg/m^3 =	303 000 kg

* Value taken from the Michigan State Department of Agriculture.
** Marsh and Campling, 1970.
*** Montfort et al., 1999.
† These are the same dimensions used in an environmental assessment of ivermectin done by Fort Dodge Animal Health (1997).