Health & Ecological Risk Assessment

Flexing the PECs: Predicting Environmental Concentrations of Veterinary Drugs in Canadian Agricultural Soils

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ABSTRACT

Veterinary drugs administered to food animals primarily enter ecosystems through the application of livestock waste to agricultural land. Although veterinary drugs are essential for protecting animal health, their entry into the environment may pose a risk for nontarget organisms. A means to predict environmental concentrations of new veterinary drug ingredients in soil is required to assess their environmental fate, distribution, and potential effects. The Canadian predicted environmental concentrations in soil (PECsoil) for new veterinary drug ingredients for use in intensively reared animals is based on the approach currently used by the European Medicines Agency for VICH Phase I environmental assessments. The calculation for the European Medicines Agency PECsoil can be adapted to account for regional animal husbandry and land use practices. Canadian agricultural practices for intensively reared cattle, pigs, and poultry differ substantially from those in the European Union. The development of PECsoil default values and livestock categories representative of typical Canadian animal production methods and nutrient management practices culminates several years of research and an extensive survey and analysis of the scientific literature, Canadian agricultural statistics, national and provincial management recommendations, veterinary product databases, and producers. A PECsoil can be used to rapidly identify new veterinary drugs intended for intensive livestock production that should undergo targeted ecotoxicity and fate testing. The Canadian PECsoil model is readily available, transparent, and requires minimal inputs to generate a screening level environmental assessment for veterinary drugs that can be refined if additional data are available. PECsoil values for a hypothetical veterinary drug dosage regimen are presented and discussed in an international context. Integr Environ Assess Manag 2017;13:331–341. © 2016 Her Majesty the Queen in Right of Canada. Integrated Environmental Assessment and Management published by Wiley Periodicals, Inc. on behalf of SETAC. Reproduced with the permission of the Minister of Health.

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INTRODUCTION

Veterinary medicinal ingredients (VMIs), a chemically diverse group of compounds, are essential for protecting animal health and well-being but can potentially have negative impacts on nontarget organisms when released into the environment (Boxall 2004; Sarmah et al. 2006). VMIs are widely used in Canadian livestock production for the treatment and prevention of diseases and parasites, and to increase feed efficiency and growth (Sarmah et al. 2006). Unlike drugs used in human medicine, which generally undergo some form of wastewater treatment, most VMIs enter terrestrial ecosystems directly as a result of animal-rearing operations (Boxall 2004). Although losses from the point of manufacture or from feed mills as a result of blending may contribute to the environmental presence of veterinary drugs (Kümmerer 2010), the majority of VMI residues in the environment originate from on-farm agricultural use patterns (Pope et al. 2009). VMIs enter the environment in the feces and urine of agricultural livestock, either directly from grazing animals or when manure is used as fertilizer (Boxall et al. 2003). The soil is therefore the most immediately exposed environmental compartment, although VMIs may also leach into groundwater or enter surface waters in runoff from fields and pastures (Sarmah et al. 2006). A wide range of VMIs, including antibiotics and parasiticides, have been detected in Canadian soils and surface waters (Floate et al. 2005; Lissemore et al. 2006; Forrest et al. 2011).

VMIs, like many plant protection products released into the environment through agricultural activities, are designed to interact with specific receptors that will confer toxicity against taxonomic groups such as bacteria and fungi (Boxall 2004), but in some cases they can also interact with and change physiological functions in vertebrates and invertebrates...
(Fent et al. 2006; Corcoran et al. 2010). These properties are highly desirable when treating diseases and infestations, or optimizing performance in livestock production facilities; however, VMI residues may have unpredictable effects in nontarget organisms (Boxall 2004). As such, it is prudent to assess potential environmental effects of newly developed VMIs, particularly before their use in intensive animal-rearing operations. A screening level estimate of the potential for exposure to a VMI in the soil compartment is an essential component of environmental risk assessments and ensures that ecotoxicity and fate testing can be appropriately targeted. Measured environmental concentrations are not available for newly developed VMIs before their commercial availability, hence a screening level calculation that generates predicted environmental concentrations (PECs) in soil (PECsoil) for new VMIs based on Canadian agronomic and husbandry practices is needed. This method needs to be readily available and transparent, and require minimal input parameters. The PECsoil should provide a conservative estimate of VMI concentrations, based on realistic worst-case assumptions appropriate for Canadian production systems, that can be refined if additional data are available.

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) was launched in 1996 by the United States, Japan, and the European Union (VICH 2014). VICH is a program for regulatory authorities and industry stakeholders to facilitate the harmonization of technical requirements for veterinary product registration. Canada does have observer status under VICH, but it is not a signatory and has not adopted the VICH guidelines for environmental assessment (Robinson 2007). VICH guidelines for the environmental assessment of new veterinary drugs (VICH 2000, 2004) are aimed at aligning requirements for veterinary product registration among VICH signatories and are also intended to serve as a basis for harmonization of VMI registration in other regions (Robinson 2007). Predicted environmental concentrations of VMIs in soil are a pivotal starting point for screening new VMIs for further environmental assessment under VICH.

VICH signatories were unable to reach consensus on a mathematical algorithm for calculating PECs (Robinson 2007; de Knecht et al. 2009) and recognized that animal husbandry and land use practices unique to a country or region needed to be considered in developing PECsoil models and defaults (VICH 2000). Production practices are variable, due to regional differences in climate, soil conditions, and crops, but also in response to drivers such as shifts in livestock prices, consumer preferences, regulations, and market access. Models to estimate a PECsoil for veterinary drugs used in confined animal husbandry have been developed for two of the VICH regions: by the European Medicines Agency for the European Union (European Medicines Agency [EMA] 2008) and by the Animal Health Institute for the United States (Animal Health Institute Environmental Risk Assessment Working Group [AHI], Guidance for industry for environmental risk assessment covering new animal drug applications for veterinary use, draft 10, unpublished works). The AHI and EMA (2008) PECsoil calculations are based on the common uniform approach originally developed by industry (Spaepen et al. 1997). These models estimate the soil concentration of a VMI intended for confined animals based on the species, the dose in relation to body weight, the length of treatment, and the quantity of manure produced and incorporated into a unit of agricultural land to a uniform depth over 1 year. The AHI PECsoil calculation has not been made public because it was developed and is owned by AHI, but it uses methodology traditionally accepted by the US Food and Drug Administration for environmental assessments. By contrast, the EMA PECsoil equation for VICH Phase I assessments of new VMIs is readily available (EMA 2008), has undergone intensive review by industry and regulatory stakeholders (EMA 2007), and can be adapted to regional animal husbandry and land use practices (Robinson 2007). The EMA PECsoil equation has also been found to approximate or overestimate measured environmental concentrations of VMIs (Metcalfe et al. 2008), and adaptation of the European PECsoil equation (EMA 2008) was therefore deemed to be the most appropriate basis for developing a Canadian screening level PECsoil for environmental assessment of VMIs (Eqn. 1).

\[
\text{PECsoil} = \frac{D \times Ad \times BW \times P \times NA}{1500 \times 10000 \times 0.05 \times Ny \times H} \times 1000, \quad (1)
\]

where PECsoil is estimated in microgram per kilogram (µg/kg), \(D\) = daily dose of VMI (mg·kg body weight\(^{-1}\)·day\(^{-1}\)), \(Ad\) = number of days of treatment (days), \(BW\) = animal body weight (kg), \(P\) = cycles (animals·place\(^{-1}\)·year\(^{-1}\)), \(NA\) = maximum nitrogen (N) application rate (kg N/ha), 10000 = area conversion factor (m\(^2\)/ha), 1500 = bulk density of dry soil (kg/m\(^3\)), 0.05 = depth of penetration into soil (m), \(Ny\) = manure N excretion rate (kg N·place\(^{-1}\)·year\(^{-1}\)), \(H\) = housing factor (fraction of time housed inside), and 1000 = conversion factor (µg/mg).

The concentration of a VMI in soil is a result of the dosage regimen and route of administration in the species treated, as well as animal husbandry and manure management and application practices (Spaepen et al. 1997; Pope et al. 2009). Even though Canadian animal production methods, crops, and manure management practices differ substantially from those that predominate in the European Union (Intergovernmental Panel on Climate Change 1996; Ontario Ministry of Agriculture, Food and Rural Affairs 2003; Whiting and Pasma 2008), an abundance of technical information is available to facilitate the adaptation of the EMA PECsoil approach. Development of the Canadian PECsoil defaults for intensively reared cattle, swine, and poultry is described in this study. Predicted environmental concentrations for VMIs in soil for a hypothetical VMI dosage regimen, a comparison with approaches in other jurisdictions, and refinements that can be made during the assessment process are also presented.

**METHODS**

The PECsoil represents the estimated concentration of a VMI in soil after treatment according to label instructions of animals in a confined animal-rearing facility over a period of
1 year. It is based on a conservative total residue approach and assumes that the highest label dose appropriate for a particular animal and VMI is given, the entire dose administered is excreted unchanged, no degradation of the VMI occurs during manure storage, and the manure is applied to agricultural lands at the maximum recommended rate. The defaults for the Canadian PECsoil were developed by leveraging a number of sources, including the Canadian Census of Agriculture (Statistics Canada 2011), the National Inventory Report: Greenhouse Gas Sources and Sinks in Canada Part 2 (Environment Canada 2013), provincial manure and fertilizer management recommendations, the scientific literature, and producer organizations.

**Animal categories**

Animal subcategories (Table 1) were developed based on an analysis of label information for veterinary drugs currently approved for sale in Canada (Health Canada Drug Product Database [HC DPD] and the Compendium of Veterinary Products [CVP]), as well as Canadian animal husbandry and agricultural practices for pigs (Prairie Swine Centre 2000; Robinson 2008), poultry (Leeson and Summers 2000; American Society of Agricultural and Biological Engineers [ASABE] 2010; Environment Canada 2013), and cattle (Boadi et al. 2004; Canada Beef 2012; Kumar et al. 2012).

**Annual production cycles**

Animals within a given category may have multiple complete production cycles per year (Table 1), during each of which the animals may be treated with VMIs. The PEC calculation is based on the quantity of nitrogen in manure produced per “place” in a production system and the number of animals that occupy that place over the course of 1 year. Animals with production cycles longer than 1 year, such as dairy cows or sows, have a default cycle of 1. Some livestock categories, such as broiler chickens or grower-finisher pigs, require less than 1 year before they complete a full production cycle and a new cohort takes their place. Each cohort may be treated with VMIs and the dosage therefore needs to be multiplied by the number of cycles per year to obtain the total volume of a VMI that is administered annually per production place. Where more than 1 production cycle is completed per year the default number of production cycles is based on the average cycle length reported in the scientific literature and/or by producer organizations for cattle (Boadi et al. 2004; Canada Beef 2012; Kumar et al. 2012; Fédération des producteurs de bovins du Québec 2013), pigs (Prairie Swine Centre 2000), and poultry (Young et al. 2010). Where cycles per year or turnover rates were directly reported, the reported value was taken as is. Downtime occurs between cycles for cleaning and disinfection of production facilities.

### Table 1. Default Canadian cattle, swine, and poultry production cycles, body weights, manure nitrogen excretion rates, and average annual proportion of time spent in housing for calculation of a predicted environmental concentration in soil for veterinary medicinal ingredients.

| Livestock production category | Cycles (animals/ place·year⁻¹) | Animal body weight (kg) | Manure N excretion rate (kg N · place⁻¹·year⁻¹) | Housing factor |
|------------------------------|--------------------------------|------------------------|-----------------------------------------------|---------------|
| Calves (<1 year)             | 1                             | 196.0                  | 14.59                                         | 0.5           |
| Calves (veal)                | 2.2                           | 169.0                  | 12.58                                         | 1             |
| Dairy cattle                 | 1                             | 637.0                  | 80.08                                         | 0.8           |
| Cattle >1 year (reproductive)| 1                             | 613.5                  | 45.68                                         | 0.5           |
| Beef cattle >1 year          | 2                             | 566.5                  | 42.18                                         | 1             |
| Piglets (10 per litter; 0–3 weeks) | 14.2 | 33.5<sup>a</sup> | 12.98                                         | 1             |
| Sows (with litter)           | 2.3<sup>b</sup>               | 192.0                  | 7.65                                          | 1             |
| Starter pigs (3–10 weeks)    | 6.6                           | 12.5                   | 1.99                                          | 1             |
| Grower-finisher pigs (>10 weeks) | 3.3 | 65.0                  | 4.68                                          | 1             |
| Broiler chickens             | 7                             | 0.9                    | 0.17                                          | 1             |
| Broiler breeders             | 1                             | 2.2                    | 0.42                                          | 1             |
| Laying hens                  | 1                             | 1.8                    | 0.26                                          | 1             |
| Turkeys                      | 3                             | 6.8                    | 1.29                                          | 1             |

<sup>a</sup>Total weight of 10 piglets.

<sup>b</sup>Farrowing cycles year⁻¹ · sow⁻¹.

<sup>c</sup>N excretion of sow and litter.
Where the number of cycles per year was inferred by the cycle length, additional downtime was not assumed.

**Body weights**

Body weights represent mature adult stages for reproductive animals and the midpoint between starting and ending weights for growing animals within each discrete production cycle. Body weights for beef and dairy cattle, with the exception of veal calves, were calculated as an average of the provinces and weighted by the respective provincial cattle subcategory population (Boadi et al. 2004). Where more than 1 value is given for a single province, they were averaged. Body weights for bob and milk- and grain-fed veal calves (Boadi et al. 2004, Government of Canada 2013) were weighted by the prevalence of the respective production method (Fédération des producteurs de bovins du Québec 2013) to obtain an average body weight for veal calves in Canada. Body weight defaults are provided for sows (ASABE 2010), piglets (de Grau et al. 2005; Environment Canada 2013), and starter and grower-finisher pigs (Environment Canada 2013). Piglet body weights are reported on a per litter basis assuming an average of 10 piglets (Prairie Swine Centre Inc. 2000). With the exception of broiler breeders (Leeson and Summers 2000), average poultry body weights are based on data from the National Inventory Report: Greenhouse Gas Sources and Sinks in Canada Part 2 (Environment Canada 2013).

**Daily feed and water intake**

Many drugs are administered in medicated feed or drinking water, and a daily dose in milligrams per kilogram body weight can be calculated based on average daily feed or water intake and the drug label information. Feed intake rates were derived from midcycle dry matter intake rates (ASABE 2010) for each animal category. Dry matter intake values were converted to a finished feed intake per kilogram body weight basis assuming 88% dry matter content in feed (Table 2). Drinking water intake rates are midcycle intake values (Agriculture and Agri-Food Canada 2009) and were converted to per kilogram body weight intake rates (Table 2) based on the default body weights for the Canadian PECsoil (Table 1).

**Housing factor**

The PECsoil equation assumes that the entire administration and excretion of the veterinary drug takes place while the animal is in housing. The housing factor represents the proportion of the year spent in a confined facility and not on pasture (Table 1). In Canada, industrial pig and poultry production takes place primarily indoors; pig and poultry animal categories therefore have a housing factor of 1. Cattle typically spend at least a portion of the year grazing on pasture with housing factors depending on the cattle category (Environment Canada 2013).

**Manure nitrogen excretion rates and storage losses**

Nitrogen in manure/slurry is used as a proxy for the amount of livestock waste produced by an animal and subsequently applied to agricultural lands. Default manure N excretion rates represent the total annual (inorganic and organic) N in manure produced per animal place in an animal production system per year and take into account N losses during storage, housing, and handling. The default values for annual N excretion rates were derived from the Statistics Canada (2006) daily N excretion coefficients for livestock. Units were converted from N excreted per 1000 kg of animal body

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**Table 2. Daily drinking water and daily feed intake rates per kilogram body weight for intensively reared cattle, swine, and poultry**

| Livestock production category | BW (kg) | DDW *(L·kg BW⁻¹·day⁻¹)* | DF *(kg·kg BW⁻¹·day⁻¹)* |
|-------------------------------|---------|--------------------------|-------------------------|
| Calves (<1 year)              | 196     | 0.11                     | 0.03                    |
| Calves (veal)                 | 169     | 0.09                     | 0.02                    |
| Dairy cattle                  | 637     | 0.11                     | 0.04                    |
| Cattle >1 year (reproductive) | 613.5   | 0.06                     | 0.02                    |
| Beef cattle >1 year           | 566.5   | 0.08                     | 0.07                    |
| Piglets (10 per litter; 0–3 weeks) | 33.5 | 0.34                     |                         |
| Sows                          | 192     | 0.13                     | 0.02                    |
| Starter pigs (3–10 weeks)     | 12.5    | 0.24                     | 0.06                    |
| Grower-finisher pigs (>10 weeks) | 65 | 0.13                     | 0.04                    |
| Broiler chickens              | 0.9     | 0.18                     | 0.08                    |
| Laying hens                   | 1.8     | 0.07                     | 0.07                    |
| Turkeys                       | 6.8     | 0.07                     | 0.05                    |

*aAgriculture and Agri-Food Canada (2009).*

bASABE (2010).

BW = body weight; DDW = daily drinking water; DF = daily feed intake.
weight per day to N excreted per place per year. The yearly manure N excretion rates for piglets and lactating sows were summed together because they occupy the same farrowing stall at the same time, and a separate N excretion rate for sows not housed with piglets is also provided. N excretion rates were adjusted for loss during storage and in housing. The N loss fractions for different manure management systems, reported in the 2013 edition of the National Inventory Report: Greenhouse Gas Sources and Sinks in Canada (Environment Canada 2013), weighted by the relative percentage of manure managed with these systems, were multiplied by the kilogram N per place per year excretion rates to derive “as applied” rates.

Nitrogen application rate and incorporation depth

Recommended N application rates were obtained from a survey of provincial fertilizer rate recommendations (Supplemental Data Tables S1, S2, and S3). Provincial guidelines recommend different fertilization rates depending on variables such as soil type, previous crop, proximity to surface water, and the ratio of fertilizer cost to crop price. The maximum recommended application rates were selected from each range to establish a conservative estimate of application rates in Canada. Provincialy recommended N application rates are based on available (i.e., inorganic) N, whereas N excretion rates are based on total N. The weighted average application rate was converted to total N (inorganic and organic) based on the assumption that approximately 35% of manure N is either in organic form or unavailable for crops (Environment Canada 2013). The N application rate of 183 kg N/ha in the Canadian PECsoil equation assumes that all N will be supplied by manure and represents an average of maximum recommended application rates for the 13 most important Canadian nonlegume field crops, tame or seeded pasture, and hay and fodder crops (Tables S1 and S3) weighted by the respective land area under cultivation (Statistics Canada 2011).

A default incorporation depth of 5 cm (0.05 m) for manure is assumed, which represents surface application with no tillage or injection. The default incorporation depth multiplied by the default soil bulk density of 1500 kg/m³ and an area of 1 ha represents the mass of soil that a veterinary drug in applied manure is assumed to be diluted by.

RESULTS AND DISCUSSION

A screening level PECsoil for a VMI intended for use in Canada can be calculated by substituting into Equation 1 the dose per kilogram body weight, the treatment duration, an N application rate of 183 kg N/ha, and the appropriate defaults for the respective livestock species and production category for which the drug is intended (Table 1). The EMA PECsoil calculation does not provide the defaults needed to calculate a daily dose for drugs that are administered in feed or water. Many VMIs approved for sale in Canada are administered in this manner (CVP 2013; HC DPD 2013), and a daily dose is a required input for the PECsoil. Canadian defaults for daily feed and drinking water intake were therefore developed (Table 2) and can be used together with information from the drug label to estimate a daily dose. PECsoil values for a hypothetical VMI administered to calves, dairy cows, grower-finisher pigs, and broiler chickens at a dose of 1 or 5 mg/kg body weight over 1, 3, or 7 days, respectively, are presented in Table 3. Although the PECsoil increases linearly with dose and duration of administration within each production

| Livestock production category | Ad (days) | 1 mg · kg BW⁻¹ · day⁻¹ | 5 mg · kg BW⁻¹ · day⁻¹ |
|------------------------------|-----------|-------------------------|------------------------|
| Calves (<1 year)             | 1         | 6.6                     | 32.8                   |
|                              | 3         | 19.7                    | 98.3                   |
|                              | 7         | 45.9                    | 229.4                  |
| Dairy cattle                  | 1         | 2.4                     | 12.1                   |
|                              | 3         | 7.3                     | 36.4                   |
|                              | 7         | 17                      | 84.9                   |
| Grower-finisher pigs         | 1         | 11.2                    | 55.9                   |
|                              | 3         | 33.6                    | 167.8                  |
| Broiler chickens             | 7         | 78.3                    | 391.4                  |
|                              | 1         | 9.1                     | 45.3                   |
|                              | 3         | 27.2                    | 135.8                  |
|                              | 7         | 63.4                    | 316.8                  |

Ad = administration duration; BW = bodyweight; PECsoil = predicted environmental concentrations in soil.
category, there are noteworthy differences in the predicted values between production categories. The PECsoil for broiler chickens, for example, is considerably higher than that for dairy cows, despite the much higher body weight of the cow, because broiler chickens have 7 annual production cycles and dairy cows have 1. This results in broiler chickens receiving 7 treatments of VMIs over the course of 1 year versus only 1 for dairy cows. The number of animals raised per production place per year is not the sole determinant of the magnitude of the PECsoil. For example, the PEC for dairy cows is also much lower than the PEC for calves even though they are the same species and both have a production cycle of 1 (Table 3). Calves have a housing factor of 0.5 compared with 0.8 for dairy cows, but this does not fully account for an almost 3 times greater PECsoil. Dairy cows are much heavier but also excrete more than twice the amount of N per kilogram body weight as calves do (Table 1). Based on an identical N application rate of 183 kg N/ha, relatively more manure from calves can be applied to fields, resulting in more VMIs reaching the soil compartment and hence a relatively higher PECsoil.

Predicted environmental concentrations in soil for a hypothetical drug dosage regimen of 5 mg/kg body weight administered for 3 days and calculated with the respective defaults and equations for the European Union (EMA 2008), the United States (AHI, unpublished works), and Canada are shown in Figure 1. The PECsoil estimates for Canada fall within the same range as those for Europe and the United States, but it is difficult and not appropriate to make direct comparisons among the 3 regions. Production classes are defined differently, encompassing variable body weight ranges and production cycle lengths, and manure and nutrient tracking approaches vary. For example, the US PECsoil calculation has a single production category for pigs that does not correspond directly to any of the European (EMA 2008) or Canadian pork production classes. The manure application rate for the US PECsoil varies with the respective animal species and is quantified in terms of freshly excreted manure mass rather than N (AHI, unpublished works). Both Canada and the EMA use a single application rate in kilogram of N per hectare as a proxy for the amount of manure applied and account for N losses during storage and housing. The N application rate for the European PECsoil is based on a regulatory limit for protection of surface waters from nitrates (EMA 2008), whereas the Canadian application rate represents a weighted average of maximum provincial recommendations for the top 13 forage-fodder and non-legume field crops by land area (Table S1) and can be updated if agricultural practices change.

The EMA PECsoil model (EMA 2008) and the defaults and categories developed for Canada have several other notable differences. The rationale for these divergences is based on differences in the agricultural and regulatory environments in the 2 regions. For example, weaning piglets younger than 28 days is prohibited by European regulations unless the health of the dam or piglets is at risk (Council Directive 2008/120/EC 2008), whereas the weaning age for piglets reared in Canada, where most producers practice segregated early weaning (isowean), may occur as soon as 16 to 17 days after birth (Whiting and Pasma 2008). Differences also exist in the relative importance of production classes and manure management systems. Europe has large dairy operations, most of which use liquid manure systems, and a comparatively small beef cow herd, which is predominantly grass fed and not usually finished in a feedlot (Intergovernmental Panel on Climate Change 1996). Canada has a comparatively small dairy cow population, a substantial beef cow herd, and large, intensively managed feedlot finishing operations, and cattle manure is predominantly stored as a solid (Environment Canada 2013).

Production classes developed for Canada were based on a careful analysis of the HC DPD (2013) and drug labels in the CVP (2013), as well as Canadian animal husbandry practices.
Age and/or body weight groups, or both, that frequently receive discrete dosages on drug labels and that correspond to specific production classes in confined animal-rearing operations were placed in separate categories. The Canadian dairy cattle category is intended for female dairy cattle that have reproduced at least once. The category for reproductive cattle older than 1 year represents all other cattle that are intended for breeding, including dairy heifers and actively breeding nondairy cattle. Beef cattle intended for feedlots are in a separate category for nonreproductive animals older than 1 year because they have a greater number of cycles and different body weights. The length of the period that an animal spends in a feedlot depends on the animals’ age and weight when it enters the feedlot, the desired final weight, and the respective breed. Lighter animals may be backgrounded after weaning to increase their frame size and sent to a feedlot for finishing at later stages, whereas larger calves are often finished directly (Kumar et al. 2012). Beef cattle, including backgrounders, spend a minimum of 4 months in a feedlot (Canada Beef 2012), and direct finishers may be in feedlots for up to 8 months (Boadi et al. 2004), resulting in an average of 6 months or 2 production cycles per year. Calves were divided into cattle younger than 1 year andveal calves because of differences in body weights, production practices, and cycle lengths. Veal calves may be slaughtered as bob calves or at 5 to 7 months ofage for milk-fed or grain-fed calves, respectively (Fédération des producteurs de bovins du Québec 2013). The cycle length for veal calves is a weighted average of the duration of the respective production method and the proportion ofbob and grain- and milk-fed veal calves in Quebec, which produces close to 80% of all Canadian veal (Fédération des producteurs de bovins du Québec 2013).

Multisite production, in which age-segregatedcohorts of animals are reared in geographically separate locations, is the predominant pork production method in North America, but it has not been widely adopted in Europe (Whiting and Pasma 2008). The Canadian PECsoil has 5 possible defaults for pork production classes compared with 3 for the EMA (2008) guidance. The default number of cycles for drugs intended for sows under EMA (2008) is 1 and includes piglets, whereas the Canadian PECsoil provides 2 different cycle defaults for sows and an option to calculate a separate PECsoil for VMI intended for administration to piglets only (Table 1). Several drugs currently approved for sale in Canada are specific to a sow’s reproductive cycle (CVP 2013; HC DPD 2013), and a default cycle of 1 would not adequately reflect the amount of VMI that are administered over the course of a whole year in a typical swine production facility. The default number of annual cycles for sows being treated for ailments not related to reproduction is 1, because they are generally kept for more than 1 year. The default number of cycles for sows treated with drugs specific to reproduction or to treat piglets through their mother’s milk is 2.3, the average number of litters per female per year (Prairie Swine Centre 2000). The Canadian PECsoil defaults provide an option to calculate a PECsoil for piglets alone, because some currently approved Canadian drug products are intended for use in piglets only (CVP 2013; HC DPD 2013). Sows produce an average of 10 live piglets per litter, and farrowing stalls are occupied by an average of 14.2 litters per year (Prairie Swine Centre 2000). Because the PECsoil calculation is based on the amount of a VMI used per place in a production facility, a default of 14.2 cycles per year is realistic for drugs used in piglets only. Which default is most appropriate for calculating a PECsoil for a new drug depends on the treatment regimen outlined in the label instructions for the VMI. The lactating sow and her piglets occupy the same stall at the same time, even if they are treated separately, and therefore have a combined N excretion rate.

Laying hens and broiler breeders generally have production cycles that are longer than 1 year (Leeson and Summers 2000; ASABE 2010); the default number of cycles is therefore 1. The production cycle default of 7 per year for broiler chickens is based on a survey (Young et al. 2010) representing a quarter of all regulated Canadian poultry producers (Diarra and Malouin 2014). Turkey hens and toms are reared separately and require different lengths of time to mature, also varying according to whether they are marketed as turkey broilers, whole birds, or for further processing. The cycle time of 3 per year for turkeys therefore represents an average (Manitoba Turkey Producers 2013; Turkey Farmers of Canada 2013).

The default manure N excretion rates for the Canadian PECsoil represent the total (inorganic and organic) N produced per animal space per year and take into account N losses during storage and housing. Manure N excretion rates are based on daily N excretion coefficients developed by Statistics Canada (2006) to estimate Canadian livestock manure production rates and have also been used to create the Canadian Agricultural Nitrogen Budget model (Yang et al. 2007). An alternative source for N coefficients for North America was considered (International Panel on Climate Change 2006), but because coefficients specific to Canada were available they were deemed more appropriate. For adaptation of the EMA 2008 PECsoil to other regions, where region-specific N excretion rates are not available, the IPCC reports can provide a good starting point. N excretion rates also had to be adjusted for loss of N caused by leaching and volatilization during storage and housing.

Manure is applied to land as fertilizer based on the nutrient requirements of the crop and available soil reserves of N and phosphorus (P). The majority of manure applied to agricultural land in Canada comes from cattle (72%) and dairy (12%) operations, followed by pork (9%) and poultry (3%), with the remainder coming from minor species (Statistics Canada 2006). More than 60% of cattle and pig manure applied is in the liquid form; the remainder is applied in liquid form (Statistics Canada 2012). Traditionally, crop requirements, limits, or both for N have determined the amount of manure applied, but excess P accumulation after repeated applications can be an environmental concern, especially in areas of Ontario, Quebec, and British Columbia with intensive pork production (Bailey and Buckley 1998). Either N or P can serve as a proxy for the amount of manure applied relative to the quantity of...
VMI administered (Spaepen et al. 1997). N was chosen as the proxy for the Canadian PECsoil because the majority of provinces provide manure management recommendations that are predominantly N based (Table S3). The manure N application rate of 183 kg N/ha represents an average of the maximum recommended rates for the top 13 forage-fodder and nonlegume field crops grown in the 8 most important crop-producing provinces weighted by land area (Tables S1 and S3). Maximum recommended rates were chosen rather than averages or regulatory upper limits to ensure a realistic yet conservative N application rate for a screening level assessment. Regional, crop-specific, or less conservative screening level assessments can be carried out by substituting the default N application rate of 183 kg N/ha with the appropriate value (Tables S1 and S2). The manure N default and the supplemental values provided should be updated if fertilizer input recommendations, which are driven by economic forces as well as agricultural practices and environmental concerns, change.

The most recent Canadian Census of Agriculture results indicate that 44% of liquid and 39% of solid-composted manure is not injected or incorporated and is left on the field surface (Statistics Canada 2011). Incorporation of solid manure is not possible on fields with perennial crops such as hay or forage, which comprise more than 30% of the total agricultural land area (Statistics Canada 2011), or if the freshly applied manure is too wet (Haak 2016). On more than half of all fields where manure is eventually incorporated it remains on the surface, where VMIs are subject to increased runoff due to precipitation (Al-Rajab et al. 2015; Kay et al. 2005), for 5 days or more after application (MacKay and Hewitt 2010). A default incorporation depth of 5 cm (0.05 m) for manure is therefore assumed, which represents surface application with no tillage or injection.

A default soil bulk density of 1500 kg/m$^3$ is used in the PECsoil calculation because of its history of standard use in screening level PECsoil calculations in Canada, Europe, and the United States for both veterinary drug and pesticide screening levels (Spaepen et al. 1997). European PECsoil pasture defaults (EMA 2008) for beef cattle (6.6 g/kg soil) than European PECsoil pasture (2.8 g/kg soil). However, the Canadian PECsoil intensive is more conservative (6.6 µg/kg soil) than PECsoil values calculated with the European PEC pasture defaults (EMA 2008) for beef cattle (4.2 µg/kg soil). The Canadian PECsoil for intensively reared animals, for a dose of 1 mg/kg body weight for 1 day, is more conservative (6.6 µg/kg soil) than PECsoil values calculated with the European PEC pasture defaults (EMA 2008) for beef cattle (4.2 µg/kg soil). However, the Canadian PECsoil intensive is more conservative (6.6 µg/kg soil) than the European PECsoil pasture (2.8 µg/kg soil). European stocking densities are based on reports from The Netherlands where pastures are managed very intensively,
and the rich soils and long growing season can support high densities of grazing animals (Montforts 1999, 2003). Stocking densities in Canada vary widely, depending on pasture or rangeland condition, region, management, and farm type, and it would be difficult to establish default values that are generally acceptable. Canadian default stocking rates and consequently pasture PECs are also likely to be much lower than the EMA defaults due to the greater available land area and less intensive pasture management. Because grazing by dairy cattle is very limited and the PECsoil for intensively reared animals is generally more conservative, development of a separate PECsoil for grazing cattle was deemed to be unnecessary.

CONCLUSIONS
The development of Canadian defaults and production classes for the European PECsoil model (EMA 2008) provides a convenient screening tool for identification of VMIs that require further assessment of potential environmental effects or to generate input values for models that predict ground and surface water concentrations caused by leaching or runoff. A spreadsheet for calculating the Canadian PECsoil and a daily dosage for drugs administered in feed or drinking water has been included in Appendix S2. The PECsoil defaults and production classes take into account Canadian agricultural practices and provide a rapid and transparent method to generate country-specific exposure estimates for VMIs that can be refined if additional information is available. Agricultural practices frequently change in response to factors such as new production methods, regulations, disease outbreaks, and economic forces such as commodity, feed, fertilizer input, or livestock prices and consumer demand. Because of the transparency with which the defaults have been developed, the Canadian PECsoil model can easily be updated to reflect these changes in agricultural practices. The Canadian PECsoil is aligned with international approaches to assessing environmental exposure and can serve as a template for adaptation of the EMA (2008) PECsoil model in other regions. A consistent approach to environmental assessment of VMIs provides practical and economic benefits and can improve access to new veterinary drugs in smaller markets such as Canada. Although the EMA (2008) PECsoil estimates appear to be conservative relative to measured environmental concentrations (Blackwell et al. 2005; Metcalfe et al. 2009; Pope et al. 2009), the newly developed Canadian production categories and defaults still need to be validated to confirm that they generate conservative exposure estimates. A validation of the overall PECsoil approach and the new defaults developed for Canada with measured environmental concentrations is currently being conducted and will be presented in a follow-up study.

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Data availability—The data for this research are publicly available. Sources are listed in the references.

SUPPLEMENTAL DATA
Supplemental Table S1. Provincially recommended maximum N application rates that can be used for province-specific assessment scenarios and values on which default application rate in this study is based.
Supplemental Table S2. Provincially recommended average and minimum N application rates that can be used for less conservative assessment scenarios.
Supplemental Table S3. Sources (provincial guidelines) for provincial fertilizer recommendations for top 13 crops in Canada.
Supplemental Table S4. Body weight ranges (starting and ending weight) for the typical Canadian livestock production categories can be used to adjust PECsoil defaults for specific treatment scenarios (i.e., drug given at beginning of cycle only).

Appendix S1. Supplemental references for fertilizer recommendations and animal body weights.
Appendix S2. PECsoil calculator.

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