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Review

Chemical use in salmon aquaculture: A review of current practices and possible environmental effects

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A B S T R A C T

The World Wildlife Fund is facilitating a dialogue on impacts of salmon aquaculture. The goal of the dialogue is to establish the state of knowledge in seven subject areas associated with the industry: benthic impacts, nutrient loading, escapees, chemical inputs, diseases, feeds and social issues and to establish international standards for salmon aquaculture practices. Chemical inputs from salmon aquaculture include antifoulants, antibiotics, parasiticides, anaesthetics and disinfectants. The use and potential effects of these compounds are herein summarized for the four major salmon producing nations: Norway, Chile, UK and Canada. Regulations governing chemical use in each country are presented as are the quantities and types of compounds used. The problems associated with fish culture are similar in all jurisdictions, the magnitude of problems is not and the number of compounds available to the fish farmer varies from country to country. Unfortunately, the requirement to publically report chemical use is inconsistent among countries. Chemical use data are available from Norway, Scotland and parts of Canada. The government of Chile and some Canadian provinces, while requiring that farmers report disease occurrence, compounds prescribed and quantities used, do not make this information readily available to the public. The fact that these data are available from regulatory agencies in Scotland and Norway adds pressure for other jurisdictions to follow suit. Data such as these are essential to planning and conducting research in field situations.

Contents

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1. Introduction

According to the United Nations Food and Agriculture Organization (FAO), salmon is farmed in 24 countries. The major producers of salmon are Norway, Chile, Scotland and Canada. Salmon production In Chile and Norway (1,152,388 MT (MT) in 2007) account for over 80% of total farmed salmon production (1,378,874 MT) (FAO, 2010). The three most common species of cultured salmon are the Atlantic salmon (*Salmo salar*) the chinook salmon (*Oncorhynchus tshawytscha*), and the coho salmon (*Oncorhynchus kisutch*). In aquaculture the Atlantic salmon represents 90% of production.

Farmed salmon are most commonly grown in large, floating cages or pens in semi-sheltered coastal bays or sea lochs. The cage systems allow release of nutrients, pathogens, and chemical inputs to the marine environment.

Chemical inputs from aquaculture activities may include prescribed compounds (pesticides and drugs), antifoulants, anaesthetics and disinfectants.

As is the case in all animal food production systems, it is often necessary to treat farmed fish for diseases and parasites. The types of therapeutants available for use and the treatment protocols are tightly regulated in all jurisdictions and they can only be used under prescription from a licensed veterinarian. As health threats have appeared, management practices have evolved and fish husbandry has greatly improved over the past 20 years resulting in a reduction in the use of some chemicals, particularly the use of antibiotics in most jurisdictions. However, fish farmers still rely on aggressive use of chemotherapeutants to combat bacterial infections and infestations of ecto-parasites as well as disinfectants to manage spread of diseases (Haya et al., 2005). In the 1990s several reviews were prepared regarding chemical inputs (see, for example Zitko, 1994; GESAMP 1997). In addition, recent publications have addressed specific issues related to use of therapeutants (see for example, Haya et al., 2005; Cabello, 2006; Sapkota et al., 2008).

There is a significant potential for salmon farms to affect local waters, especially if poorly sited or poorly managed. Of particular concern is the potential for chemical inputs to affect the diversity of the local fauna commonly referred to as non-target organisms and for the selection of antibiotic resistance to develop in microbes. This review addresses the current status of the use of chemicals in the aquaculture industry. We focus on the four major salmon producing nations: Norway, Chile, Scotland, and Canada. Research gaps are identified and recommendations presented.

2. Therapeutants

2.1. Antibiotics

Antibiotics are designed to inhibit the growth (bacteriostatic activity) and kill pathogenic bacteria (bacteriocidal activity). Compounds with antibiotic activity are selected for use in human and veterinary medicine because of their selective inhibition of the synthesis of the cell wall and other membranes, macromolecular synthesis or enzyme activity in prokaryotic cells (Guardabassi and Courvalin, 2006; Alekshun and Levy, 2007; Nikaido, 2009; Todar, 2008). As a result of these selective traits they show low or very low toxicity in higher organisms (Guardabassi and Courvalin, 2006; Alekshun and Levy, 2007; Nikaido, 2009; Todar, 2008).

The following is a summary of products that are or have been reported to be used to treat bacterial infections in salmon aquaculture:

Amoxicillin is a broad spectrum antibiotic from the β-lactam class. It is effective against gram positive and gram negative bacteria used in the aquaculture industry to treat fish with infections of *Furunculosis* (*Aeromonas salmonicida*). It acts by disrupting peptidoglycan synthesis, a component of the bacterial cell wall (Guardabassi and Courvalin, 2006; Alekshun and Levy, 2007; Todar, 2008). The recommended treatment is 80–160 mg (active ingredient) kg^{-1} (fish) for 10 days presented on medicated food. There is a 40–150 day (DD) withdrawal period in Scotland. A degree day is the cumulative number of centigrade temperature units (1-day equals an average water temperature of 1 °C for 24 h) (Jensen and Collins, 2003). The β-lactams should be susceptible to biological and physiochemical oxidation in the environment since they are naturally occurring metabolites. (Armstrong et al., 2005). Bacterial genetic determinants encoding β lactamases with the potential to inactivate amocixillin are shared by fish and human pathogens (McIntosh et al., 2008).

Florfenicol is also a broad spectrum antibiotic used to treat salmon against infections of *Furunculosis*. It is part of the phenicol class of antibiotics which act by inhibiting protein synthesis (Guardabassi and Courvalin, 2006; Alekshun and Levy, 2007; Todar, 2008). The recommended treatment regime is 10 mg kg^{-1} for 10 days presented on medicated food. The withdrawal period for florfenicol is 12 days in Canada, 150 DD in Scotland and 30 days in Norway. The concentration (in water) which is expected to be lethal to 50% of an exposed population over 96 h (96 h LC50) of florfenicol is >330 mg L^{-1} (*Daphnia*) and >780 mg L^{-1} (rainbow trout). This product is not generally considered a problem for persistence in the environment but resistance may develop and its genetic determinant can be shared by fish and human pathogens (Arcangioli et al., 1999; Briggs and Fratamico, 1999; Angulo, 2000; Armstrong et al., 2005; Doublet et al., 2005; Miranda and Rojas, 2007).

Tribrissen (sulfadiazine: trimethoprin (5:1)) is a combination of sulphonamide and trimethoprim that is a broad spectrum antibacterial agent used to treat salmon infected with gram negative bacteria such as *Furunculosis* and *Vibrios* (*Vibrio anguillarum*, for example). It acts by inhibiting folic acid metabolism at two different levels (Guardabassi and Courvalin, 2006; Todar, 2008). The recommended treatment regime is 30–75 mg kg^{-1} for 5–10 days presented on medicated food. The withdrawal period is 350–500 DD in Scotland and 40–90 days Norway. The environmental impact of use of this product is unknown but given its broad spectrum and the fact that may be degraded slowly it may affect bacteria of the marine sediments and fish pathogens selecting for resistance (Kim and Aoki, 1996; Armstrong et al., 2005) The genetic determinants for resistance to this class of antibiotics (sulfas) are found in fish and human pathogens (Ceccarelli et al., 2006; Osorio et al., 2008). This product is rarely used in salmon aquaculture as salmon do not appear to eat pellets medicated with Tribrissen (M. Beattie, Province of New Brunswick, personal communication).

Oxolinic acid and flumequin are quinolone antibiotics used to treat organisms against infections of gram negative bacteria such as *Piscirickettsia salmonis*, *Furunculosis* and *Vibrio* infections. These products inhibit DNA replication (Guardabassi and Courvalin, 2006; Todar, 2008). The recommended dose of these compounds for Atlantic salmon is 25 mg kg^{-1} for 10 days (applied on medicated food) and a withdrawal period of 500 DD has been set for Scotland, although these products are no longer used in that country. In Norway the withdrawal period ranges from 40–80 days depending on water temperature. These products are highly effective but persist in the environment (Armstrong et al., 2005). Plasmid encoded genetic determinants for quinolones resistance with potential clinical relevance have been identified in marine bacteria such *Shewanella*, *Vibrio* and *Aeromonas* (Poirel et al., 2005a,b; Cattoir et al., 2007; Cattoir et al., 2008) and they are also found in human pathogens (Jacoby et al., 2009). The importance of this class of antibiotics in human medicine has led to a prohibition of their use for treating salmon in Scotland, Canada and the United States.

Oxytetracycline is a broad spectrum antibiotic active against infections of *Furunculosis* and *Vibrio* (Powell, 2000). This tetracycline antibiotic is delivered on medicated food at dosages ranging from 50–125 mg kg^{-1} applied over 4 to 10 days. Tetracyclines act by inhibiting protein synthesis (Guardabassi and Courvalin, 2006; Todar, 2008). The withdrawal time prior to marketing fish is 400–500 DD in Scotland and 60–180 days in Norway (Armstrong et al., 2005). The compound has a low toxicity (96 h LC50 for fish is >4 g kg^{-1}). It has a relatively high water solubility however, as it is bound to food pellets it can become bound to sediments and may be persistent for several hundred days complexed to ions and with decreased antibacterial activity (Armstrong et al., 2005). The combination of low toxicity and broad spectrum effectiveness has led to the widespread overuse and misuse in human and animal health and therefore to the development of resistance and reduced effectiveness (Guardabassi and Courvalin, 2006; Todar, 2008). Genetic determinants of resistance to tetracyclines are shared by fish and human pathogens (Sørum, 1998; Rhodes et al., 2000; Furushita et al., 2003; Miranda et al., 2003; Sørum, 2006; Roberts, 2009).

Erythromycin is a macrolide antibiotic useful in combating gram positive and non-enteric gram negative bacteria responsible for causing Bacterial Kidney Disease (Powell 2000). It is presented on medicated food at dosages ranging from 50–100 mg kg^{-1} for 21 days. Erythromycin inhibits genetic translation, therefore protein synthesis (Guardabassi and Courvalin, 2006; Todar, 2008). It has a low toxicity to fish (96 h LC0>2 g kg^{-1}) but can accumulate in sediments and organisms and is a concern in terms of antibiotic resistance. This antibiotic is not approved for salmon aquaculture use in countries which belong to the International Council for the Exploration of the Seas (ICES). This includes Norway, Scotland and Canada. It is, however listed as an approved compound in Chile (Pablo Forno personal communication).

Despite their low toxicity, there are significant environmental concerns with widespread use of antibiotics. Many antibiotics are stable chemical compounds that are not broken down in the body but remain active long after being excreted in stool and urine and after passing to the environment with uningested food (Capone et al., 1996; Hektoen et al., 1995; Boxall et al., 2004; Aarestrup, 2006; Sørum, 2006) These antibiotics may have decreased antibiotic activity if they bind to organic matter in the sediments and its activity is affected by high salt concentrations and pH (Smith et al., 1994). Antibiotics may affect the biological diversity of the phytoplankton and the zooplankton communities (Holten Lützhøft et al., 1999; Christensen et al., 2006; Gonçalves Ferreira et al., 2007). These changes in diversity potentially may affect the health of animals and humans (Morris, 1999; Van Dolah, 2000; Cabello, 2004) and are potentially detrimental to the salmon aquaculture industry. At present, antibiotics make a considerable contribution to the growing problem of active medical substances circulating in the environment. They increase the possibility of selection of antibiotic resistant determinants and bacteria that may affect animals and humans (Boxall et al., 2004; Sarmah et al., 2006; Wright, 2007; Baquero et al., 2008; Martinez, 2009; Silbergeld et al., 2008). Resistance to antibiotics in the aquatic environment results from selection of spontaneous mutants by antibiotics in the environment and by horizontal gene transfer and its stimulation between different species and genera including marine bacteria, human and fish pathogens (Alonso et al., 2001; Hastings et al., 2004; Sørum, 2006; Aarestrup, 2006; Welch et al., 2007; Baquero et al., 2008; Silbergeld et al., 2008; Martinez, 2009). In general, the more an antibiotic is used, the greater the risk of emergence and spread of resistance against it as a result of increased selective pressure, thus rendering the drug increasingly useless (Levy, 2001, 2002; Schwarz et al., 2006; Aarestrup, 2006). The contribution of the use of antibiotics in aquaculture to the selection of antibiotic resistance and its dissemination among different bacteria and environments including human pathogens has not been determined (Smith et al., 1994; Smith, 2008; Heuer et al., 2009). However, the commonality of genetic determinants for antibiotic resistance between bacteria of the marine environment and the terrestrial environment including fish and human pathogens suggest that this contribution may be relevant and that horizontal gene transfer takes place rather fluidly between these apparently isolated populations (Briggs and Fratamico, 1999; Miranda et al., 2003; Hastings et al., 2004; Sørum, 2006; Aarestrup, 2006; Welch et al., 2007; Baquero et al., 2008; Osorio et al., 2008; Silbergeld et al., 2008; Martinez, 2009; Roberts, 2009). Multiple resistant bacteria can also be selected in aquaculture by the deposition in the marine sediment of metal ions, i.e. copper, zinc, mercury (see below) (Akinbowale et al., 2007; McIntosh et al., 2008).

The most severe consequence is the emergence of new bacterial strains that are resistant to several antibiotics simultaneously (Levy, 2002; Aarestrup, 2006; Baquero et al., 2008). In human health and animal health infections caused by such multi-drug resistant pathogens present a special challenge, resulting in increased clinical complications and death that previously could have been treated successfully. This may result in longer hospital stays and significantly higher costs to society (Cosgrove et al., 2002; Mølbak, 2006; Maragakis et al., 2008; MacGowan et al., 2008). The worst scenario is that dangerous pathogens will eventually acquire resistance to all previously effective antibiotics, thereby giving rise to uncontrolled epidemics and epizootics of bacterial diseases that can no longer be treated (Levy, 2001, 2002; Hawkey, 2008) The safety of human food can also directly be affected by the presence of residual antibiotics in farmed fish which have been dosed with antibiotics (Grave et al., 1999; Cabello, 2003, 2006; White and McDermott, 2009). For example, in 2007 the FDA of the United States had to block temporarily the sales of five aquaculture products from China because they contained salmonella and, among other residues, nitrofurans and fluorquinolones (New York Times, 2007a,b). Antibiotics used in aquaculture can also reach wild fish and shellfish surrounding aquaculture sites and collected for human consumption, therefore potentially affecting food safety (Samuelsen et al., 1992; Coyne et al., 1997; Fortt et al., 2007). Furthermore, application of large quantities of antibiotics can also affect the health of workers employed in feed mills and on cage sites as a result of dust aerosols containing antibiotics that have been created in the process of medicating and distributing the feed to fish (Cabello, 2003, 2006). Inhalation, ingestion and contact of the skin of workers with these aerosols will alter their normal flora, select for antibiotic-resistant bacteria and potentially generate problems of allergy and toxicity (Anderson, 1992; Salyers et al., 2004; White and McDermott, 2009; Cerniglia and Kotarski, 2005).

Antibiotics in salmon aquaculture, as in other industrial husbandry of aquatic and terrestrial food animals including other fish, shrimp, cattle and poultry, are used as therapeutic agents in the treatment of infections (Alderman and Hastings, 1998; Angulo, 2000; Sørum, 2000, 2006; Pillay, 2004; Silbergeld et al., 2008). Veterinarians are duty-bound to treat sick animals. There is no evidence that antibiotics are used as growth promoters in aquaculture as is the case in the industrial raising of cattle, poultry and hogs in some countries (Alderman and Hastings, 1998; Davenport et al., 2003). It is relevant to mention here that according some authors (Stead and Laird, 2002; Beveridge, 2004; Austin and Austin, 1999), an animal husbandry industry that uses excessive antibiotics and other chemicals to fend off infectious diseases is an industry in permanent crisis. Excessive antibiotic use in industrial animal rearing, by selecting for antibiotic resistance pathogens, ultimately has the potential of backfiring and negatively affecting all the aspects of the industry including its economic health.

It is incumbent upon farmers to practice husbandry techniques that promote healthy “livestock” and thereby reduce the need for antibiotic treatments. The need to use large quantities of antibiotics is, in general, the result of shortcomings in rearing methods and hygienic conditions that favor animal stress, opportunistic infections and their dissemination (Teuber, 2001; Wassenaar, 2005; Silbergeld et al., 2008).

These findings have resulted in regulations directed at curtailing the use of antibiotics in terrestrial animal farming in Europe and North America (Grave et al., 1999; Wierup, 2001; Teuber, 2001; Angulo et al., 2004). These regulations have led to restriction of antibiotic use in animal husbandry in many countries but have not resulted in increased costs to the industry and have been shown to be compatible with profitable animal farming (Grave et al., 1999; Wierup, 2001; Prescott, 2006).

Antibiotic inputs from salmon aquaculture vary widely. For example in Chile in the years 2007 and 2008, according the Chilean Government, 385.6 and 325.6 MT were used in salmon aquaculture respectively, to produce between 300,000 and 400,000 metrics tons of Atlantic salmon (Ministerio de Economia de Chile, 2009; FAO, 2010). In the same years the industry in Norway used less than a metric ton of these drugs to produce larger amounts of salmon than Chile, approximately 820,000 MT (Table 1). Approximately, 150 MT of these antibiotics included the quinolones, oxolinic acid and flumequine (Ministerio de Economia, Chile, 2009). Importantly, regarding the biological effects of these antibiotics is that in Chile these amounts are used in a geographical area that is approximately one fourth of that in Norway (Buschmann et al., 2006). For these reasons, it appears as though there is considerable room for improvement in terms of reducing the quantities of these products that are being delivered to the aquatic environment in some jurisdictions.

2.1.1. Regulation and reporting of antibiotic use by country

2.1.1.1. Norway. Norway is the largest producer of farmed Atlantic salmon in the world (821,997 MT in 2007 (FAO, 2010)). Norway regulates antibiotic use in aquaculture. These regulations have led to a significant reduction in the classes and volumes of antibiotics used (Sørum, 2006; Grave et al., 1996; Lillehaug et al., 2003; Markestad and Grave, 1997). These regulations were implemented as the result of extensive research in Norway and other countries which indicated that the excessive use of antibiotics was deleterious to many aspects of aquaculture, the environment, and potentially to human health as discussed above.

The volume of antibiotic use in aquaculture is closely monitored by a centralized regulatory agency through monitoring of veterinary prescriptions originating from aquaculture sites (Lillehaug et al., 2003; Markestad and Grave, 1997). This links antibiotic use to defined geographical areas, references timing of application and permits rapid detection of any increases in use. The end effect of this effort is not only the control of antibiotic use but also detection of misuse (prophylactic use, for example), and most importantly, early detection of emergence of potentially epizootic and devastating salmon infections (Grave et al., 1996; Sørum, 2006; Grave et al., 1999). Close monitoring decreases the possibility of excessive use of antibiotics and allows initiation of rapid mitigating measures such as isolation, quarantine, implementation of physical barriers and fallowing of sites. The control of antibiotic use in aquaculture in Norway, the use of hygienic measures in fish rearing, and the introduction of effective vaccines have permitted the Norwegian aquaculture industry to reduce its use of antibiotics to negligible amounts despite its increasing output (Grave et al., 1999; Lillehaug et al., 2003).

Table 1 shows the products used in the salmon aquaculture industry in Norway, Chile and Scotland and the volumes applied from 2006 to 2008. While some authors suggest only antibiotics that are not considered relevant for human medicine can be used in aquaculture (Grave et al., 1999; Sørum, 2000, 2006; Grave et al., 1996; Lillehaug et al., 2003; Markestad and Grave, 1997), oxolinic acid, a quinolone, is used in salmon aquaculture in Norway.

Table 1
Antibiotic use in Norway and Scotland 2006–2008. Quantities are reported in kg of active ingredient. Source: Norwegian Institute of Public Health (2009) and Scottish Environmental Protection Agency.

Antimicrobial	Country	2006	2007	2008
Oxytetracycline	Norway	0	19	23
	Scotland	5282	1532	75.4
Florfenicol	Norway	302	139	166
	Scotland	32	21	9
Flumequin	Norway	7	18	1
Amoxycillin	Scotland	55.2	0	0
Oxolinic acid	Norway	1119	406	681
Lincomycin/streptomycin (1:2)	Norway	50	67	70

2.1.1.2. Chile. Chile is the second largest producer of farmed salmon in the world (380,391 MT in 2007 (FAO, 2010)). Bravo (personal communication) reports that the following antimicrobial products are registered for use in Chile: oxolinic acid, amoxicillin, erythromycin, flumequine, florfenicol, and oxytetracycline. Producers are required to report incidence of disease, the products prescribed for treatment and quantities used. The government agencies did not, until recently, make this information public. Bravo et al. (2005) report total antibiotic use in salmon aquaculture in 2003 to be 133,000 kg. This is equivalent to 0.47 kg of antibiotics applied for every metric ton of fish produced. Recently antibiotic use has been reported as 385,600 kg in 2007 and 325,600 kg in 2008 (Ministerio de Economia, Chile, 2009). Atlantic salmon production in 2007 and 2008 was 330,391 MT and 388,048 MT respectively (FAO, 2010). The FAO reports salmon production for Chile to be 330,391 in 2007 (FAO, 2010).

Application of large quantities of antibiotics in the aquaculture industry in Chile has been partially justified by the presence of pathogens that do not pose problems in other countries such *P. salmonis* (Brocklebank et al., 1993; Branson and Diaz-Munoz, 1991; Olsen et al., 1997; Perez et al., 1998; Mauel and Miller, 2002; Reid et al., 2004). *P. salmonis* is a preferentially intracellular emergent pathogen that infects salmon smolt after they are moved from fresh water to the marine environment. The infection is thought to be enabled by the stress of transport and introduction to sea water (Barton and Iwama, 1991). Infections by this pathogen produce large economical losses in the Chilean aquaculture industry (Brocklebank et al., 1993; Branson and Diaz-Munoz, 1991; Perez et al., 1998; Mauel and Miller, 2002; Reid et al., 2004), and to date there is no effective commercially available vaccine to prevent these infections. However, this pathogen has been detected in the United States, Canada, Ireland, Scotland and Norway where *P. salmonis* outbreaks appear to be small, sporadic and readily controlled by husbandry measures without any use of antibiotics. Moreover, there are no studies indicating that *P.*

salmonis is in fact susceptible the antibiotics (including quinolones) used in salmon aquaculture in Chile (Olsen et al., 1997; Perez et al., 1998). However, now that *P. salmonis* can be cultured studies addressing the sensitivity of *P. salmonis* should be forthcoming (Mikalsen et al., 2008; Mauel et al., 2008).

The fact that *P. salmonis* is apparently able to live in seawater without causing infection to healthy fish and that its major targets are potentially stressed post-smolt salmon strongly suggests that this pathogen is an opportunist (Olsen et al., 1997; Perez et al., 1998; Mauel and Miller, 2002). In human public health and in the husbandry of animals it has been extensively shown that the prevention of infections by opportunistic pathogens is better achieved by hygienic measures than by the use of antibiotics as prophylactics (Prescott, 2006; Wheatley et al., 1995). The large amounts of antibiotic used in Chile to apparently prevent opportunistic infections of *P. salmonis*, suggests that most of the antibiotics may have been used prophylactically to forestall the negative consequences of limiting sanitary conditions demonstrated by the wide and rapid spread of the ISA virus (Godoy et al., 2008; Kibenge et al., 2009).

Recently the National Fisheries Service (Sernapesca) announced the initiation of a monitoring program regarding the use of antibiotics in salmon production. The hope is to diminish the use of fluoroquinolones since they are antibiotics of the latest generation and needed most importantly in human medicine and to reduce the possibility of development of antibiotic resistance (Fish Farming Expert, 2008). As it has recently been done, it is expected that in Chile in the future data about the use of antibiotics may be made available to the public.

Bravo and Midtlyng (2007) have reported the use of fish vaccines in Chile. Their data show a trend towards use of vaccines compared to antibiotic treatment. Unfortunately, the effectiveness of a recently marketed vaccine against *P. salmonis* is still unproven in the field.

2.1.1.3. Scotland. Scotland is the third largest producer of farmed Atlantic salmon (132528 MT in 2007). Antibiotic products and volumes used in the salmon aquaculture industry in Scotland from 2006 to 2008 are shown in Table 1.

Prescriptions must be written, discharge consents granted and monthly reports must be made to the Scottish Environmental Protection Agency (SEPA). The data are easily accessible to the public. As a result, it is easy to determine if use patterns of a specific compound. For example, the use of oxytetracycline was over three times greater in 2006 than in 2005. This increase is a result of increased application in a small area as opposed to widespread application throughout the industry (SEPA, 2009). Farmers and regulators can use this information to make decisions regarding disease status and measures that need to be taken to address the disease and the use of the antibiotic.

2.1.1.4. Canada. Canada is the fourth largest producer of farmed Atlantic salmon and the largest North American producer (102,509 MT in 2007 (FAO, 2010)).

The following products are registered for use as antibiotics in Canada: Oxytetracycline, trimethoprim80%/sulphadiazine20%, sulfadimethoxine80%/ormetoprim20%, and florfenicol. Table 2 shows the quantities of antibiotic actually applied in Canada from 2006 to 2007 and in British Columbia (BC) only in 2008. While BC produces the majority of Atlantic salmon grown in Canada, there is a significant salmon aquaculture industry on Canada's east coast.

Table 2
Total antibiotic use (kg active ingredient) in Canada and Chile.

Total antibiotics	2006	2007	2008*
Canada[a]	13,522	21,330	5093
Chile	NA	385,600	325,600

[a]Data for the provinces of British Columbia and New Brunswick or for *British Columbia only. Data are not available for other Canadian provinces.

Since so few compounds are available in Canada and even fewer are actually applied (M. Beattie, Province of New Brunswick, personal communication) there may be reason for concern regarding resistance development. Without data about what compounds are applied, and where, it is difficult to assess risk. Recently the Province of New Brunswick, on Canada's east coast, instituted regulations wherein incidence of disease, products applied to combat disease and quantities used must be reported monthly. It is anticipated that in 2010 edited summaries of these reports will be available to the public (M. Beattie, Province of New Brunswick, personal communication). This will provide data on therapeutant usage with temporal and spatial context.

2.2. Parasiticides

Cultured salmon are susceptible to epidemics of infectious bacterial, viral and parasitic diseases. Sea lice are ecto-parasites of many species of fish and have been a serious problem for salmon aquaculture industries (Roth et al., 1993). The species that infest cultured Atlantic salmon are *Lepeophtheirus salmonis* and *Caligus elongatus* in the northern hemisphere and *Caligus teres* and *Caligus rogercresseyi* in Chile. Infestations result in skin erosion and sub-epidermal haemorrhage which, if left untreated would result in significant fish losses, probably as a result of osmotic stress and other secondary infections (Wootten et al., 1982; Pike, 1989). Sea lice reproduce year round and the aim of successful lice control strategy must be to pre-empt an internal infestation cycle becoming established on a farm by exerting a reliable control on juvenile and pre-adult stages, thus preventing the appearance of gravid females (Treasurer and Grant, 1997). Effective mitigation, management and control of sea lice infestations require good husbandry and often treatment with antiparasitic compounds.

Compounds used to treat infestations of sea lice are applied under veterinary prescription and are ultimately released to the aquatic environment. Anti-lice treatments lack specificity and therefore may affect indigenous organisms, in particular crustaceans, in the vicinity of anti-lice treatments. Sea lice therapeutants, via their effects not only have the potential to negatively impact sensitive non-target organisms by altering the population structure within the immediate surroundings (Johnson et al., 2004). The release of these compounds has been identified as a major environmental concern (Nash, 2003). The therapeutants or classes of therapeutants currently used to combat sea lice infestations are: avermectins, pyrethroids, hydrogen peroxide and organophosphates (Haya et al., 2005; Bravo et al., 2005; Lees et al., 2008).

These compounds may be classified into two groups based on their route of administration, bath treatments and in-feed additives. Pyrethroids, hydrogen peroxide and organophosphates are or have been administered by bath techniques, while avermectins are administered as additives in feed.

2.2.1. Avermectins

The avermectins are effective in the control of internal and external parasites in a wide range of host species, particularly mammals (Campbell, 1989). In invertebrates, they generally open glutamate-gated chloride channels at inhibitory synapses resulting in an increase in chloride concentrations, hyperpolarization of muscle and nerve tissue, and inhibition of neural transmission (Roy et al., 2000; Grant, 2002). Avermectins can also increase the release of the inhibitory neurotransmitter γ-amino-butyric acid (GABA) in mammals.

In the past, ivermectin was used to treat infestations of sea lice in salmon (Burridge, 2003). Currently the only avermectin used is emamectin benzoate (EB; SLICE®), a semi-synthetic derivative of a chemical produced by the bacterium, *Streptomyces avermitilis*. EB is used in all jurisdictions. Until 2009 EB was used in Canada under an emergency drug release but it now has full registration status (Richard Endris, Intervet Corporation, personal communication). The optimum therapeutic dose for EB is 0.05 mg kg^{-1} fish day^{-1} for seven consecutive days (Stone et al., 1999), which has been shown to be effective in removing lice of all developmental stages (Stone et al., 2000a,b).

EB also has low water solubility and relatively high octanol–water partition coefficient, indicating that it has the potential to be absorbed to particulate material and surfaces and that it will be tightly bound to marine sediments with little or no mobility (SEPA, 1999a). The half-life of EB is 193.4 days in aerobic soil and 427 days in anaerobic soil (SEPA, 1999a). In field trials, EB was not detected in water samples and only 4 of 59 sediment samples collected near a treated cage had detectable levels. The EB persisted in the sediment; the highest concentration was measured at 10 m from the cage 4 months post-treatment. In Canada, however, EB was not detected in sediment samples collected near an aquaculture site for the 10 weeks immediately after treatment with SLICE® (W.R Parker, 2003, Environment Canada, unpublished report). Mussels were deployed and traps were set out to capture invertebrates near aquaculture sites undergoing treatment. While detectable levels of EB and metabolites were measured in mussels (9 of 18 sites) one week after treatment, no positive results were observed after 4 months (SEPA, 1999a). EB was found in crustaceans during and immediately after treatment. Species showing detectable levels for several months after treatment are scavengers which are likely to consume faecal material and waste food (SEPA, 1999a).

2.2.1.1. Biological effects of emamectin benzoate. The treatment concentrations in salmon feed range from 1 to 25 μg kg^{-1} (Roy et al., 2000) Feeding EB to Atlantic salmon and rainbow trout at up to ten times the recommended treatment dose resulted in no mortality. However, signs of toxicity, lethargy, dark coloration and lack of appetite were observed at the highest treatment concentration (Roy et al., 2000).

The effects of EB-treated fish feed on non-target organisms have been reported by a number of authors (Linssen et al., 2002; Waddy et al., 2002; Willis and Ling, 2003; Burridge et al., 2004). The compound is not lethal to organisms tested to date at recommended treatment concentrations. Waddy et al. (2002) reported that ingestion of EB induced premature molting of American lobsters. This molting response of lobsters may involve an inter-relationship of a number of environmental (water temperature), physiological (molt and reproductive status) and chemical (concentration/dose) factors (Waddy et al., 2002). Further studies of this response suggest that the risk may be limited to a small number of individuals and that widespread population effects are unlikely (Waddy et al., 2007).

Overuse or over-reliance on any single compound can lead to the development of resistance to the compound in the parasite (SEARCH, 2006). Not surprisingly, evidence of resistance has recently been reported in Chile (Bravo, 2009). Canada limits the number of sea lice treatments with EB during a grow-out cycle to 3, while up to 5 treatments may take place during the grow-out cycle in Norway and the UK and in Chile between 4 and 8 treatments may take place. Only one EB-based product is used in Norway, Scotland and Canada. Several products have been used in Chile (Bravo et al., 2008; Bravo, 2009).

2.2.2. Pyrethroids

The synthetic pyrethroids cypermethrin (Excis and Betamax) and deltamethrin (AlphaMax, Pharmaq) are topical (bath) treatments. Pyrethroids have relatively high degradability, low toxicity to mammals and high toxicity to crustaceans (Davis, 1985). The mechanism of action of the pyrethroids involves interference with nerve membrane function, primarily by their interaction with sodium channels which results in depolarization of the nerve ending (Miller and Adams, 1982).

The recommended treatment of salmon against sea lice is a 1 h bath with Excis® at a concentration of 5.0 μg L^{-1} (as cypermethrin), 30 min with Betamax® (15 μg L^{-1} as cypermethrin) and for deltamethrin it is 2.0–3.0 μg $L^{-1}$for 40 min (SEPA, 1998b) The pyrethroids are effective against all attached stages of the louse including adults.

Synthetic pyrethroids are unlikely to be accumulated to a significant degree in aquatic food chains since they are rapidly metabolized (Kahn, 1983). This author warns, however, that pyrethroids such as cypermethrin can persist in sediments for weeks and may be desorbed and affect benthic invertebrates.

Several authors have reported that the concentration of cypermethrin in water collected from within and around cages after treatment is low (Hunter and Fraser, 1995; SEPA, 1998b; Pahl and Opitz, 1999). Cypermethrin was only occasionally detectable 100 m from treated cages. Shrimp (*Crangon crangon*) were deployed in cages at various distances and depths from the cages during treatment with cypermethrin at two salmon aquaculture sites in Scotland during treatment with cypermethrin. The only mortalities were to shrimp held in treated cages (SEPA, 1998b). Shrimp in drogues released with the treated water were temporarily affected but recovered (SEPA, 1998b). In an American field study, cypermethrin was lethal to 90% of the lobsters in the treatment cage but no effect was observed in those located 100–150 m away. There was no effect observed in mussels placed outside or inside the cages. Similar field studies indicated that cypermethrin was lethal to lobsters and planktonic crustaceans in the treatment tarpaulin but not to mussels, sea urchins or planktonic copepods.

2.2.2.1. Biological Effects of pyrethroids. The biological effects of pyrethroids and other anti louse therapeutants have been reviewed recently by Haya et al. (2005). Not surprisingly, in lab-based studies arthropods are very sensitive to these compounds whereas molluscs, echinoderms and fish tend to be less sensitive (see for example, McLeese et al., 1980; Burridge and Haya, 1997; Burridge et al., 1999, 2000a,b).

The fate and dispersion of cypermethrin and the dye rhodamine were determined after simulated bath treatments from a salmon aquaculture site under various tidal conditions in the Bay of Fundy, Canada (Ernst et al., 2001). Dye concentrations were detectable for 2–5.5 h, and distances ranging from 900 to 3000 m depending on the location and tidal flow at the time of release. Concentrations of cypermethrin in the plume reached 1–3 orders of magnitude below the treatment concentration 3–5 h post release and indicated that the plume retained its toxicity for substantial period after release. Water samples collected from the plume were toxic in a 48 h lethality test to *Eohausterorus estuarius* for cypermethrin up to 5 h. Thus it appears as though single treatments have the potential to affect non-target invertebrates near cage sites. Medina et al. (2004) have reported that while cypermethrin immediately reduces plankton density and diversity in lab studies, they hypothesized that in an open system pesticide concentrations would drop quickly and that plankton migration and immigration would lead to recovery of the community. Willis et al. (2005) reported that sea lice treatments on salmon farms had no effect on zooplankton communities.

Because pyrethroids tend to adsorb onto particulate matter, chronic exposures may not occur other than in laboratory studies. Cypermethrin absorbed by sediment was not acutely toxic to grass shrimp until concentrations in sediment were increased to the point where partitioning into the overlying water resulted in acutely lethal concentrations (Clark et al., 1987).

Reliance on the use of only a few products can lead to incidence of resistance in the sea lice population. In a region of Norway where a population of resistant sea lice was identified. The concentration of deltamethrin required to successfully treat fish was 25 times higher than that for an area that had not been treated previously with deltamethrin (Sevatadal and Horsberg, 2003).

2.2.3. Hydrogen peroxide

Hydrogen peroxide is a strong oxidizing agent that was first considered for the treatment of ecto-parasites of aquarium fish (Mitchell and Collins, 1997). It is widely used for the treatment of fungal infections of fish and their eggs in hatcheries (Rach et al., 2000). With the development of resistance to organophosphates by sea lice (Jones et al., 1992) there was a move towards the use of hydrogen peroxide to treat infestations of *L. salmonis* and *C. elongatus*. Hydrogen peroxide was used in salmon farms in Faroe Islands, Norway, Scotland and Canada in the 1990s (Treasurer and Grant, 1997), and the formulations Paramove® and Salartect® are still authorized for use in all countries but it is not the treatment of choice. Hydrogen peroxide was used as an anti-louse treatment in Scotland in 2008 (SEPA, 2009) and has recently been applied in Chile (Bravo, 2009). Its use could be an indication that reduced efficacy of other products. The suggested mechanisms of action of hydrogen peroxide are mechanical paralysis, peroxidation by hydroxyl radicals of lipid and cellular organelle membranes, and inactivation of enzymes and DNA replication (Cotran et al., 1989). Most evidence supports the induction of mechanical paralysis when bubbles form in the gut and haemolymph and cause the sea lice to release and float to the surface (Bruno and Raynard, 1994).

The recommended concentration for bath treatments is 0.5 g L^{-1} for 20 min. However, the effectiveness is temperature dependent and the compound is not effective below 10 °C (Treasurer et al., 2000). Treatments are rarely fully effective but 85–100% of mobile stages may be removed (Treasurer et al., 2000). Hydrogen peroxide has little efficacy against larval sea lice and its effectiveness against pre-adult and adult stages has been inconsistent (Mitchell and Collins, 1997).

It is generally considered environmentally compatible because it decomposes into oxygen and water and is totally miscible with water. At 4 °C and 15 °C, 21% and 54% of the hydrogen peroxide decomposed after 7 days in sea water. If the sea water is aerated the amount decomposed after 7 days is 45% and 67%, respectively (Bruno and Raynard, 1994). Field observations suggest that decomposition in the field is more rapid, possibly due to reaction with organic matter in the water column, or decomposition catalyzed by other substances in the water, such as metals. This has been described in freshwater (Richard et al., 2007; Miller et al., 2009). In most countries, hydrogen peroxide is considered a low environmental risk and therefore of low regulatory priority. While other compounds are subject to a withdrawal period between time of treatment and time of harvest, hydrogen peroxide has none (Haya et al., 2005).

2.2.3.1. Biological effects of hydrogen peroxide. There is little information of the toxicity of hydrogen peroxide to marine organisms. In the lab, shrimp and bivalve molluscs survive short-term exposure to treatment concentrations (L.E. Burridge unpublished results). Most toxicity data describe the potential effects on salmonids during treatment of sea lice infestations. Experimental exposure of Atlantic salmon to hydrogen peroxide at varying temperatures demonstrated that there is a very narrow margin between treatment concentration (0.5 g L^{-1}) and that which causes gill damage and mortality (2.38 g L^{-1}) (Kiemer and Black, 1997).

Toxicity to fish varies with temperature; for example, the one hour LC50 to rainbow trout at 7 °C was 2.38 g L^{-1}, at 22 °C was 0.218 g L^{-1} (Mitchell and Collins, 1997). Its toxicity to Atlantic salmon increased five-fold when the temperature was raised from 6 °C to 14 °C. There was 35% mortality in Atlantic salmon exposed to hydrogen peroxide at 13.5 °C for 20 min. While these fish had a rapid increase in respiration and loss of balance, those exposed at 10 °C showed no effect (Bruno and Raynard, 1994). Abele-Oeschger et al., 1997 report that hydrogen peroxide causes a decrease in metabolic rate and in intracellular pH in the shrimp, *C. crangon*.

2.2.4. Organophosphates

In the past, four organophosphate compounds have been used in the treatment of infestations of sea lice: malathion, trichlorfon, dichlorvos (DDVP) and azamethiphos (Haya et al., 2005). Organophosphates are neurotoxic, inhibiting acetylcholinesterase (AChE) activity (Baillie, 1985). Currently, organophosphates are rarely used for sea lice treatments. For a number of years, DDVP was the treatment of choice against infestations of sea lice. However, frequent use led to the resistance to DDVP in sea lice in some areas (Tully and McFadden, 2000). This coupled with a small therapeutic index (dose toxic to salmon/dose used to treat sea lice) resulted in the product being phased out as an anti-louse therapeutant. Azamethiphos was also used for a number of years. Azamethiphos is an organophosphate insecticide and the active ingredient in the formulation Salmosan®. It is used as a bath treatment at a concentration of 0.1 mg L^{-1} for up to 1 h.

Azamethiphos is registered for use in Chile, Norway and Scotland. Novartis, the producer of Salmosan® did not renew the registration of their product in Canada in 2002. However, in 2009, emamectin benzoate ceased to be effective in controlling sea lice infestations in parts of southwest New Brunswick Canada and several treatment options have been explored One of these options is to again treat affected salmon with Salmosan® (M. Beattie, Province of New Brunswick, personal communication).The organophosphates DDVP and azamethiphos are soluble in water and have low octanol–water partition coefficient (Roth et al., 1993). Consequently, they are likely to remain in the aqueous phase on entering the environment and unlikely to accumulate in tissue or in sediment. The bioaccumulation of organophosphates by salmon is low and depuration in salmon is rapid resulting in short withdrawal times prior to harvesting.

2.2.4.1. Biological effects of organophosphates. The sensitivity of lice to organophosphates is variable, and some populations of lice are more sensitive to this compound than others. Development of resistance to organophosphates is common in sea lice and has been shown in all formulations developed to date (Haya et al., 2005). In sensitive populations of lice, azamethiphos is effective in removing >85% of adult and pre-adult lice but is not effective against the earlier life stages of the parasite (Roth et al., 1996).

As was the case with pyrethroids marine arthropods are the most sensitive organisms to exposure to organophosphates (Haya et al., 2005). Research commissioned by the pharmaceutical firm Ciba-Geigy shows that azamethiphos is only lethal to several groups of invertebrates (bivalve molluscs and gastropods, amphipods, and echinoderms) at concentrations greater than the prescribed treatment concentration of 100 μg L^{-1} (SEPA, 1998a). Burridge et al. (2008) have shown that repeated short-term exposures to azamethiphos can result in negative effects on survival and spawning in American lobsters.

Field studies have shown that a single treatment with the organophosphate Salmosan have no negative effect on survival of non-target organisms except when held within the treatment cage (see for example Burridge, 2003). Measurements of primary productivity and dissolved oxygen were made before, during and after drug treatments at salmon farms in southwest New Brunswick, Canada in August–September 1996. There were no evident effects on dissolved oxygen and chlorophyll *a* levels, indicating no impact on primary production (D. Wildish, St. Andrews Biological Station, St. Andrews, NB, unpublished data).

2.2.5. Chitin synthesis inhibitors

Chitin synthesis inhibitors belong to a class of insecticides collectively referred to as insect growth regulators and have been used in terrestrial spray programs for nuisance insects since the late 1970s. Two products, teflubenzuron (Calicide®) and diflubenzuron (Lepsidon®) are currently registered for use. Until recently neither product was being produced and therefore was not being used to combat infestations of sea lice (Tables 4–7). In 2007 and 2008 these compounds were used in Scotland (teflubezuron, 2007, Table 6) and Chile (diflubenzuron, 2008, Table 5). Recently a manufacturer has begun to produce Calicide® for the Canadian market and it is expected that the product will be used in New Brunswick Canada in 2009 (M. Beattie, Province of New Brunswick, personal communication).

The chitin synthesis inhibitors are effective against the larval and pre-adult life stages of sea lice. Teflubenzuron is effective against *L. salmonis* at a dose to salmon of 10 mg kg^{-1} body weight per day for 7 consecutive days at 11–15 °C (Branson et al., 2000). Since chitin synthesis inhibitors are effective against the developing copepodids, larval (chalimus) and pre-adult stages of sea lice and less effective against adult lice, treatments are most effective before adult lice appear, or at least are present in only low numbers. In some cases, a prior bath treatment with organophosphates may be useful to remove adult lice or to control recruitment. When used correctly, chitin synthesis inhibitors provide a treatment option that breaks the life cycle of the sea lice and, as a result, the duration between treatments may be several month (Haya et al., 2005).

2.2.5.1. Distribution and fate of chitin synthesis inhibitors. Teflubenzuron and diflubenzuron have moderate octanol–water partition coefficients and relatively low water solubility, which means that they tend to remain bound to sediment and organic materials in the environment. They are not persistent in freshwater (SEPA, 1999b; Eisler, 1992) and a few marine studies suggest that sediment is a significant sink for these compounds in the marine environment.

In a field study, a total of 19.6 kg of teflubenzuron was applied over a 7 day period to treat a salmon cage with a biomass of 294.6 MT (SEPA, 1999b). Teflubenzuron was not detected in the water after treatment and highest concentrations in the sediments were found under the cages and decreased with distance from the cage in the direction of the current flow. The half-life was estimated at 115 days and 98% of the total load had degraded or dispersed by 645 days after treatment (Haya et al., 2005). There was some indication of re-suspension and redistribution of sediment after several weeks based on concentrations of teflubenzuron found in mussel tissues. Evidence suggested that there was some risk to indigenous sediment dwelling crustaceans, such as crab or lobster that may accumulate teflubenzuron from the sediment. However, the mussels eliminated teflubenzuron readily.

Diflubenzuron was found to be stable and persistent in anoxic marine sediments under laboratory conditions. There was no significant decrease in concentration (38 and 50 µg g^{-1}) after 204 days for diflubenzuron in sediments held in the dark at 4 and 14 °C or in sediments in tanks that were flushed with sea water (Selvik et al., 2002). In field studies and microcosm studies diflubenzuron had a much shorter half-life than teflubenzuron (Haya et al., 2005). The half-life ranged from 4 to 17 days depending on substrate and experimental design (Haya et al., 2005).

2.2.5.2. Biological effects of chitin synthesis inhibitors. Teflubenzuron is potentially highly toxic to any species which undergo molting within their life cycle (SEPA, 1999b; Fischer and Hall, 1992).

Aquatic toxicity data for diflubenzuron has been compiled for 15 estuarine and marine species, mostly invertebrates (Eisler, 1992). The premolt stage of grass shrimp was the most sensitive to diflubenzuron (96 h LC50 = 1.1 µg L^{-1}) and the mummichog, *Fundulus heteroclitus*, was the most resistant species (96 h LC50 = 33 mg L^{-1}). Exposure of a marine harpacticoid copepod indicated that concentrations of diflubenzuron as low as 1.0 µg L^{-1} cause adult mortality and inhibited reproduction. The viability of *Acartia tonsa* nauplii to hatch was reduced to <50% during a 12 h exposure to 1 µg L^{-1} of diflubenzuron. When brine shrimp were exposed to ≥2 µg L^{-1} of diflubenzuron, the reproductive life span and numbers of broods produced were significantly less than in controls. The 96 h LC 50 to various life stages of grass shrimp are: larvae, 1.44 µg L^{-1}; post-larvae, 1.62 µg L^{-1} and adult, >200 µg L^{-1}. There was 60% mortality of the resident grass shrimp in a tidal pool treated with 45 g ha^{-1} diflubenzuron. The borrowing behavior of fiddler crab was significantly reduced by exposure for more than one week to >5.0 µg L^{-1} of diflubenzuron. However, there was 100% mortality of stone crab larvae exposed to 5.0 µg L^{-1}; 95% mortality of the blue crab exposed to >3.0 µg L^{-1}; 46% mortality of juvenile blue crab after treatment of the tidal pool to 3.6 µg L^{-1} at 1 h after treatment. The lowest reported chronic effect concentration for a saltwater organism exposed to diflubenzuron was 0.075 µg L^{-1}. This concentration was shown to significantly reduce reproduction in mysid shrimp.

In a field study, no adverse effects of teflubenzuron were detectable in the benthic macrofaunal community or indigenous crustaceans and it was concluded that residual teflubenzuron in sediment was not bioavailable (SEPA, 1999b). There was some evidence of effects on the benthic fauna within 50 m of the treated cages, but no adverse impacts on community structure and diversity including important key sediment re-worker species and crustacean populations. Evidence suggests that teflubenzuron is relatively non-toxic to sediment re-worker organisms such as polychaete worms, the environmental risks in the use of teflubenzuron in the treatment of sea lice infestations in this study were considered to be low and acceptable (Haya et al., 2005).

2.2.6. Therapeutant use by country

Therapeutant use is regulated in all countries where salmon aquaculture is practiced. A veterinary prescription is required to use these compounds. The registration procedure or the authorization of a permit to apply a therapeutant includes an assessment of the potential risk of its use. In most cases the information provided to regulatory authorities by registrants includes proprietary information, not accessible by the general public. The absence of these data from the public domain has the unfortunate consequence that neither its quality nor its nature can be debated by those scientists and non-scientists with interests in these areas. The available data pertaining to the use of antiparasitic compounds in the Norway, Chile, Scotland and Canada are shown in Table 3.

In the summer of 2009 emamectin benzoate was fully registered by Health Canada (Health Canada, 2010). In addition, deltamethrin was given an emergency drug release by Health Canada and was used in a small area of southwest New Brunswick. Finally, the registration status of azamethiphos and teflubenzuron has been reviewed with a goal of having these products available in southwest New Brunswick (M. Beattie, Province of New Brunswick, personal communication). Until 2009 emamectin benzoate has been the only product used in Canada since 2001 (Table 3).

The apparent use of only a few products and the fact that there are few products being developed for sea lice treatment should raise concerns within the industry. Even drug manufacturers stress the benefits of the availability of a suite of compounds and of the rational application of these products to avoid resistance development. In fact, several products are now being made available under emergency

Table 3
Parasiticides used and quantities applied (kg active ingredient) in Norway, Chile, Scotland and Canada the quantities used 2006–2008. Source: Norwegian Institute of Public Health (2009), Scottish Environmental Protection Agency, Bravo et al. (2005) and Sandra Bravo (personal communication October 2009).

Active compound	Country	2006	2007	2008
Cypermethrin	Norway	49	30	32
	Scotland	10.2	38.0	21.5
Deltamethrin	Norway	23	29	39
	Chile	–	5.2	105.2
Emamectin benzoate	Norway	60	73	81
	Scotland	37.2	61.8	63.5
	Chile	–	594.9	285
	Canada[a]	20.4	19.7	14.3
Azamethiphos	Norway	0	0	66
	Scotland	0	0	100.2
Teflubenzuron	Scotland	0	95.8	0
	Chile	–	0	162

[a] Canadian data are for British Columbia and New Brunswick or for British Columbia only. Data are not available for other Canadian provinces.

conditions in Canada because of a severe infestation of sealice in 2009 (M. Beattie, Province of New Brunswick, personal communication). An integrated approach to sea lice treatment similar to that employed in Scotland may have allowed the industry to avoid the apparent crisis.

3. Metals

Metals enter the marine environment from aquaculture activity either from antifoulant paints or as constituents of fish food. Metals are present in fish feed either as constituents of the meal from which the diet is manufactured or are added for nutritional purposes. The metals in feed include copper, zinc, iron, manganese, and others. Copper and zinc, from whatever source have been shown to be significantly elevated near aquaculture sites.

3.1. Copper

Copper-based antifouling paints are applied to salmon cages and nets to prevent the growth of attached marine organisms because the buildup of these organisms ("epibiota") would be expected to reduce the water flow through the cages and decrease dissolved oxygen, decrease the durability of the nets, and reduce their flotation (Braithwaite et al., 2006). The rate of release of chemicals from the paint is affected by the nature of the toxic agent, water temperature, current speed and physical location of the structure. The active ingredients in these paints leach into the water (Singh and Turner, 2008) and may exert toxic effects on non-target local marine life both in the water column and in the sediments below the cages, where the chemicals tend to accumulate. Currently, copper-based paints are the most prevalent antifoulant in use. Copper has been measured in sediments near aquaculture sites at concentrations higher than the recommended sediment quality guidelines (see for example, Burridge et al., 1999; Parker and Aube, 2002).

The toxicity of copper in water is greatly affected by the chemical form or structure of the copper ("speciation"), and to what degree it is bound to various ligands that may be in the water reducing its toxicity (Newman and Unger, 2003). The salinity and pH also affect toxicity of copper. Metals such as copper have relatively low solubility in water and tend to accumulate in sediments. The critical issue regarding toxicity of copper (and other metals) in sediments is what fraction of the copper is actually bioavailable, that is, how much can be taken up into organisms and thereby produce toxic effects. Copper associated with fish food is likely to be unavailable in the water column. Sediments under fish farms tend to be reducing, have high oxygen demand (Page et al., 2005), and sulfide levels from the animal wastes and uneaten feed (Karakassis et al., 1998). Hence, the sediments near these sites should bind metals to a high degree.

The release of antifoulants into the marine environment and their effects on water quality may be controlled by local and/or national waste discharge regulations in various countries (Costello et al., 2001). Generally elevated copper has been observed in sediments near salmon aquaculture facilities (Burridge et al., 1999). Sediment concentrations of copper below the cages in Canadian salmon farms were generally around 100–150 mg kg^{-1} dry weight, and exceeded levels that are considered "safe" (exceed sediment quality criteria) (Burridge et al., 1999; Debourg et al., 1993). In a study of British Columbia fish farms, Brooks and Mahnken (2003) found that 5 out of 14 farms had copper levels exceeding sediment quality criteria. The average Cu in reference stations was 12 μg g^{-1} dry sediment, while under farms using Cu-treated nets the average was 48 μg g^{-1}. The Cu concentrations in sediments under the salmon farms were highly variable, consequently that this difference was not statistically significant. Chou et al. (2002) similarly found that Cu was elevated under salmon cages in Eastern Canada. Copper in anoxic sediments under cages was 54 mg kg^{-1}, while in anoxic sediments 50 m away it was 38.5. Parker and Aube (2002) found that copper in sediments was elevated compared to Canadian sediment quality guidelines in 80% of the aquaculture sites they examined.

Analysis of sediments under and around many Scottish fish farms was performed by Dean et al. (2007). Pore water concentrations were 0.1–0.2 μg L^{-1} Cu. Levels decreased with distance from the cages, and background (control) levels were found in sediments about 300 m away from the farm center. The maximum level of copper in surface sediments was 805 μg g^{-1}. In contrast, the sediment quality criterion for copper in Scotland is 270 μg g^{-1}, which would indicate adverse impacts are likely.

Tissues from fish in net pen operations were analyzed for copper (Burridge and Chou, 2005). They found no accumulation in the gills, plasma, or kidneys compared to wild fish that had not been living in net pens. There was some accumulation in the liver, but it was lower than in fish from sites severely contaminated with copper from other sources, so it is less of a problem. Peterson et al. (1991) compared copper levels in muscle and liver tissue of chinook salmon grown in pens with treated nets with those from a pen with untreated nets and similarly found no significant differences. In contrast to the salmon in the pens, lobsters living in sediments in the vicinity of salmon aquaculture sites showed high accumulation of copper (Chou et al., 2002). Lobsters from the aquaculture site with the poorest flushing had accumulated 133 μg g^{-1} in the digestive gland, while those from a control site without aquaculture had only 12.4 μg g^{-1}in their digestive glands. The digestive gland, or hepatopancreas, functions like the liver and accumulates high levels of contaminants.

Brooks (2000) studied the leaching of copper from antifouling paints and found initial losses of 155 μg Cu·$(cm^2)^{-1}$ day^{-1} and that rates declined exponentially. He developed a model that suggested that the US Environmental Protection Agency (EPA) copper water quality criterion would not be exceeded when fewer than 24 cages were installed in two rows oriented parallel to the currents flowing in a maximum speed greater than 20 cm s^{-1}. If the configuration, orientation, or density of nets was changed, the water quality criterion could be exceeded, which would increase the likelihood of adverse effects from dissolved copper in the water. In contrast, Lewis and Metaxas (1991) measured copper in water inside and outside a freshly treated aquaculture cage and reported the concentrations inside were not significantly different from those outside and the levels did not decrease after one month. The concentration of copper in water in the cage was 0.54 μg L^{-1}, while it was 0.55 outside the cage and 0.37 (not significantly different) at a station 700 m away. Similar levels were found one month later.

When copper accumulates in sediments below fish pens, it does so along with fish wastes. These, in turn, elevate the organic carbon and sulfides, that bind the copper, making it generally non-available and of low risk. Because of the high sulfides and low dissolved oxygen, there is likely to be a very depauperate, low diversity community of opportunistic organisms in the sediments that is likely to be resistant to the copper (Dauer et al., 1992). Parker et al., 2003 exposed the marine amphipod *Eohaustorius estuarius* to sediments collected from under a cage site. The level of copper in the sediments was up to 5 times greater than Environment Canada's predicted effect level, but there was no apparent effect on the amphipods. The authors attribute this to the lack of bioavailability of the copper. However, disturbance of the sediments by currents could cause the sediments to be redistributed into the water column, and could re-mobilize the metals. Similarly, clean-up of the fish wastes and reduction in sulfides could make the sediment copper more available.

3.1.1. Biological effects of copper

Among the most sensitive groups to copper are the algae, molluscs and crustaceans. In fact copper is often used as an algicide or molluscicide. A number of authors have reported the toxic effects of copper on phytoplankton, the most important primary producers in the ocean (see for example, Cid et al., 1995; Franklin et al., 2001). Le Jeune et al. (2006) have shown that high copper concentrations can decrease phytoplankton diversity. Bacterial abundance has been shown to be affected in an estuarine community exposed to 10 μg L^{-1} total copper (Webster et al., 2001). Copper has been shown to be lethal to copepods and amphiopods (Borgmann et al., 1993; Bechmann, 1994) and to affect natural copepod assemblages at sublethal concentrations (Reeve et al., 1977). There can be seasonal as well as life history differences in sensitivity to copper. The acute toxicity of copper to coastal mysid crustaceans was much greater in the summer than in the winter (Garnacho et al., 2000). Sublethal responses of invertebrates to elevated copper include reduced swimming speed of barnacle larvae (Lang et al., 1980), molt delay in shrimp larvae (Young et al., 1979), decreased embryonic development of oysters (Coglianese and Martin, 1981) and changes in enzymatic activity in crabs (Hansen et al., 1992). Elevated copper from a treated net has been shown to be lethal to fish (Burridge and Zitko, 2002). In addition, Bellas et al. (2001) and Anderson et al. (1995) have reported sublethal responses in fish exposed to copper in water.

Despite the binding of copper in sediments, it can be toxic. Sediments under salmon cages in the Bay of Fundy and at various distances away from the cages were evaluated for toxicity using an amphipod toxicity test, the Microtox® (bacterial luminescence) solid phase test and a sea urchin fertilization test (Burridge et al., 1999). The Microtox® and urchin survival were very sensitive indicators of pore water toxicity. In addition to elevated levels of copper (above the threshold effects level), the sediments also had elevated zinc, other metals, ammonia nitrogen, sulfide, total organic carbon, and other organic compounds. Hence, the toxicity cannot be attributed solely to copper. Sediments enriched in copper, zinc and silver caused decreased reproduction in the clam *Macoma balthica*, due to failed gamete production. Reproductive recovery occurred when contamination decreased (from 287 to 24 μg g^{-1}) (Hornberger et al., 2000). All these studies from field sites have numerous metals rather than just copper alone, and it is difficult to attribute toxicity to any particular metal.

Studies have been performed examining the behavioral responses of burrowing organisms to Cu-contaminated sediments. Behavior is a very sensitive indicator of environmental stress that may affect survival (Weis et al., 2001). Burrowing behavior is critical for clams and other infauna for protection from predation. Burrowing time of the clam *Protothaca staminea* was increased at contamination levels above 5.8 μg g^{-1} Cu in dry sediments. Clams that had been previously exposed had a lower threshold and a longer re-burrowing time (Phelps et al., 1983). Juveniles of the bivalve *Macomona liliana* moved away from Cu-dosed sediments. Their rate of burial was lowered, and at levels above 15 mg kg^{-1} dry weight most failed to bury and exhibited morbidity by 10 days (Roper and Hickey, 1994).

There have been numerous studies indicating that organisms chronically exposed to metals may become more resistant to the metals (Klerks and Weis, 1987). This can occur through physiological mechanisms, which include induction of metal binding proteins such as metallothioneins, stress proteins, phytochelatins in plants, or sequestering the metals in metal-rich granules. Development of resistance can also occur via an evolutionary process over generations via selection for more tolerant genotypes (Klerks and Weis, 1987). This is similar to the way in which microbes become resistant to antibiotics, but development of resistance in plants and animals will take considerably longer than in microbes, due to longer generation times. Although the development of resistance, when it happens, will reduce the negative impacts of toxicants, one cannot count on its development in any particular species.

3.1.2. Antifoulant use by country

The Scottish Environmental Protection Agency (SEPA) requires annual reporting of use of antifoulant paints from each site and these data are available to the public. Table 4 shows use in Scotland from 2003 to 2006. Data on antifoulant use are not available from other jurisdictions discussed in this paper. Copper is expressed as a range rather than a single amount, since different antifouling paints contain different concentrations of copper and it is unclear from the data provided by SEPA which particular paint is being applied to the nets.

3.2. Zinc

Zinc, an essential element, is used in salmon aquaculture as a supplement in salmon feeds. Zinc, like copper, binds to fine particles and to sulfides in sediments, and even when it is bioavailable, is much less toxic than copper (Newman and Unger, 2003). Issues of speciation, bioavailability in the water column and in the sediments are similar to those for copper. Like copper, zinc has been measured in sediments near salmon aquaculture sites at concentrations which exceed sediment quality guidelines. Given the nature of sediments under salmon cages, zinc is generally considered to be unavailable to most aquatic organisms.

Concentrations of zinc in feeds produced for Atlantic salmon range from 30 to 100 mg Zn kg^{-1} (Brooks et al., 2002). However, the dietary requirements of Atlantic salmon for Zn are estimated to be lower than this, so it would appear that the metal concentrations in some feeds exceed the dietary requirements (Lorentzen and Maage, 1999). Some feed manufacturers have recently changed the form of Zn to a more available form (zinc methionine) and consequently have decreased the amount of Zn in feed to minimum levels necessary for salmon health (Nash, 2001). Levels of Zn in some diets are now extremely low. This should, with time, significantly reduce inputs to the marine environment.

Elevated zinc has been found in sediments below and around salmon cage cultures. Burridge et al. (1999) and Chou et al. (2002) found elevated zinc concentrations in sediments near aquaculture sites that frequently exceeded the Canadian threshold effects level. Zinc in anoxic sediments under cages was 258 μg g^{-1}, while 50 m away from the cages the concentration was only 90 μg g^{-1}. Parker and Aube (2002) similarly found that the average Zn concentration in sediments under salmon pens exceeded the Canadian interim sediment quality guidelines. Dean et al. (2007) found maximum levels of Zn around salmon cages in Scotland to be 921 μg g^{-1} which is more than twice the sediment quality criterion of 410 μg g^{-1} and may indicate "probably adverse" effects on the benthos. Pore water concentrations were 0.1–0.4 μg gL^{-1}. Levels of Zn decreased with distance from the fish farm, and Zn declined to background levels 300 m from the cages. In a Canadian study, zinc concentrations declined to background at >200 m from the cages (Smith et al., 2005). Brooks and Mahnken (2003) found that zinc under Canadian salmon farms ranged from 233 to 444 μg g^{-1} in sediments, generally exceeding the "apparent effects threshold" (AET) of 260 μg g^{-1} down-current 30–75 m from the cages, the zinc concentrations were down to a background of 25 μg g^{-1}. In a New Zealand salmon farm, the sediment Zn concentrations also exceeded the sediment quality criteria of 410 μg g^{-1} (Morrisey et al., 2000). Sediment zinc at the salmon farm was 665 μg g^{-1}, while at a control site it was only 18 μg g^{-1}. The Zn at the salmon farm was comparable to concentrations shown by Watzin and Roscigno (1997) to impair recruitment of benthic invertebrates.

When fish are removed from the cages ("harvested") there is a post production fallow period in which there is a decrease in the

Table 4
Reported antifoulant use (kg of copper oxide) in salmon aquaculture in Scotland from 2003–2006.
Scottish Environmental Protection Agency.

Antifoulants	2003	2004	2005	2006
Copper oxide	18,996–26,626	11,700–29,056	34,000–84,123	35,550–86,930

amounts of chemicals in the sediments ("remediation"). During this time of inactivity, the sediment concentrations of Zn and other contaminants under cages in British Columbia declined to background levels (Brooks et al., 2003). There was also a reduction in organic material and sulfide in the sediments. At the same time, the biological community, previously dominated by two opportunistic species of annelids, became more diverse, with many different species of annelids and crustaceans and molluscs recruiting into the sediments. However, in the Bay of Fundy, zinc and copper levels remained fairly constant for five years after removal of cages (Smith et al., 2005), showing site differences in remediation potential.

Disturbance of the sediments by currents or trawling could cause the sediments to be redistributed into the water column, and could re-mobilize the metals. Zinc, like copper, binds to fine particles and to sulfides in sediments, and even when it is bioavailable, it is much less toxic than copper (Newman and Unger, 2003). Under salmon cages, the sulfide levels are probably high and dissolved oxygen low (Page et al., 2005) due to the volume of salmon wastes, making most of the zinc unavailable. Organically enriched fish farm sediments generally have a high biological oxygen demand and negative redox potential; conditions that lead to sulfate reduction.

When metals in sediments decline, they must go somewhere else, since they do not get degraded. During the "remediation" fallow period discussed above, in which sediment levels of Zn may decline, the reduction of organic material and sulfide concentration would be expected to release the Zn, increasing metal bioavailability. The probable reason for the decline in metals in sediments during remediation is that the metals are released into the water column, and therefore could be more available and toxic to other pelagic organisms in the vicinity.

Most research, and all regulations, pertaining to metal release from salmon aquaculture operations is focused on near-field concentrations. Very little research has been done on the re-suspension of near-field sediments. It is known that fallowed sites usually have reduced sulfide and organic content in these sediments (Brooks et al., 2003). The question of where metals are transported to and what effect this may have in the far-field environment has not been addressed and deserves investigation.

3.2.1. Biological effects

Zinc in ionic form can be toxic to marine organisms, though generally at considerably higher concentrations than copper.

Marine algae are particularly sensitive to zinc in water. Effects on cell division, photosynthesis, ultrastructure, respiration, ATP levels, mitochondrial electron-transport chain (ETC)-activity, thiols and glutathione in the marine diatom *Nitzschia closterium* were investigated by Stauber and Florence (1990). A number of authors have reported lethal and sublethal response of invertebrates to elevated levels of zinc (see, for example Arnott and Ahsanullah, 1979; Sunda et al., 1987; Stauber and Florence, 1990; Harmon and Langdon, 1996; King, 2001).

Bellas (2005) studied effects of Zn from antifouling paints (zinc pyrithione — Zpt) on the early stages of development of the ascidian *Ciona intestinalis*. The larval settlement stage was the most sensitive, with toxic effects detected at 9 nM (EC_{10}). Based on these data, the predicted no effect concentrations of Zpt to *C. intestinalis* larvae are lower than predicted environmental concentrations of Zpt in certain polluted areas, and therefore Zpt may pose a risk to *C. intestinalis* populations.

Sediment zinc from a freshwater fish farm was studied for toxicity to the annelid *Limnodrilus hoffmeisteri* (Tabche et al., 2000). Hemoglobin, ATP, and protein concentrations were measured in worms exposed to pond sediments from three different trout farms, and to Zn-spiked sediments. Zn concentration in fish pond sediments was 0.0271–0.9754 mg kg^{-1}. All three pond sediments showed sublethal toxicity, since ATP and protein concentrations were reduced compared to that of control worms. Zn-spiked sediments also significantly reduced ATP, protein, and hemoglobin concentrations in the worms (Tabche et al., 2000).

3.3. Other metal concerns

A recent report (DeBruyn et al., 2006) indicates that mercury was elevated in fillets of native copper rockfish and quillback rockfish collected in the vicinity of salmon farms in British Columbia. The reason suggested for the increased Hg in these long-lived, demersal, slow growing fish was that the conditions fostered by the aquaculture facilities caused them to become more piscivorous and shift to a higher trophic level, thereby bioaccumulating greater amounts of mercury that was already in the ecosystem from other sources. This observation is of interest and should lead to further research into this phenomenon. Chou (2007) reported that the mercury concentration in harvested Atlantic salmon is well within the regulatory limit set by the USFDA (1.0 mg methyl mercury·kg^{-1}) and the USEPA guidance of 0.029 mg methyl mercury·kg^{-1}.

Since elevated levels of copper and zinc occur together in sediments below salmon cages, it is possible that they may interact with each other in a synergistic way to cause even more deleterious effects. In general the majority of studies have found that these two metals seldom interact synergistically with each other. While some studies have shown synergistic interactions (Herkovitz and Helguero, 1998) most studies have found either additive effects or, more often, antagonistic interactions, wherein the presence of zinc reduces the toxic effects of the copper (Finlayson and Verrue, 1982; Newman and Unger, 2003).

4. Disinfectants

The presence of infectious salmon anaemia (ISA) and the prevalence of bacterial infections in some jurisdictions have resulted in protocols being developed to limit transfer of diseases from site to site. These protocols involve the use of disinfectants on nets, boats, containers, raingear, boots, diving equipment, platforms and decking. Unlike parasiticides, there appear to be no regulations regarding the use of disinfectants. Thus, in areas around wharves or in small sheltered coves disinfectant input could be significant. There is no information on the amounts of disinfectants used by the salmon aquaculture industry or by the processing plants and the food industry, making it very difficult to determine precisely the quantities of these products used. In most cases the disinfectants are released directly to the surrounding environment. The effects of disinfectants in the marine environment appear to be poorly studied. In addition, only the UK requires reporting of quantities of disinfectants being used in aquaculture activity. All of the compounds used are quite water soluble and should be of low toxicity depending on quantities used. Risk of aquatic biota being exposed to the disinfectant formulations is dependent not only on how much is being used but where it is being released.

Table 5 shows the quantity of disinfectants used in Scotland for 2003–2008. Individual products are not identified. In Chile the following products are identified as being used in salmon aquaculture: Virkon ®, Iodine + detergents, Chloramine-T, Hypochlorite ($HClO_2$), Chlorine dioxide (ClO_2), Benzalkonium chloride, Superquats ®, Glutaraldehyde, Formalin 40%, Calcium oxide: CaO or quicklime, Calcium hydroxide; $Ca(OH)_2$ or slake lime, Sodium carbonate: Na_2CO_3 or soda ash, Creolina, Synthetic phenols, halophenols and Ethanol (95% and 70%) (Bravo et al., 2005).

Information regarding compounds for other jurisdictions is not available but it is expected the list would be similar for all areas.

Disinfectant formulations often contain surfactants of which the actual compounds used may not be listed on the label. Some of these compounds are known endocrine disruptors that affect salmon as well as other marine organisms. Without information on what compounds

Table 5
The total of disinfectants used on Atlantic salmon out sites in Scotland in 2003–2008. Scottish Environmental Protection Agency.

Year	Total quantity of disinfectants used (kg[a])
2003	19,745[b]
2004	15,345[b]
2005	405
2006	266
2007	275
2008	28,394[b]

[a] Assumes 1 L = 1 kg.
[b] Includes data for use of hydrogen peroxide. It is unclear whether this compound was used as a disinfectant or as an antiparasitic therapeutant.

are being used and in what quantities it is extremely difficult to assess risk to salmon and to non-target organisms.

5. Anaesthetics

Anaesthetics are used operationally in salmon aquaculture when fish are sorted, vaccinated, transported or handled for sea lice counts or stripping of broodstock. Compounds available for use are regulated in all jurisdictions. They are used infrequently and in low doses, thus limiting potential for environmental damage. Only Scotland and Norway require yearly reporting of anaesthetic compounds and the quantities used. These values are shown in Tables 6.

The use of anaesthetics is generally considered to be of little risk to the environment. It is likely that most of the anaesthetic used in aquaculture is used in freshwater and in transport of fish.

6. Conclusions

Detailed chemical use data are available from Norway, Scotland and parts of Canada. The government of Chile and some provinces of Canada require that farmers report disease occurrence, compounds prescribed and quantities used, but do not make this information available to the public. Risk assessment models are used in the registration process for all regulated compounds and monitoring programs are in place for chemicals in some jurisdictions (SEPA, 2006). In Scotland where use data are available interpretation of monitoring results is possible. Without data on chemical use the interpretation of monitoring data is exceedingly difficult. Most compounds used in salmon aquaculture are highly regulated and significant quantities of data are supplied to the regulatory agencies. A considerable amount of discussion, ill feeling and contention could be avoided if these data were more accessible to the public.

The report prepared for the WFF salmon aquaculture dialogue was reviewed by a number of people from within and outside the industry. Comments from these reviewers show a variety of opinions. Several reviewers suggested that salmon aquaculture is held to a higher standard than other food producing industries. The authors are not in a position to make this judgement. We conclude, however, that public release of available data would eliminate much of the disagreement and contention that exists. The fact that these detailed use data are available from regulatory agencies in Scotland and Norway adds pressure for other jurisdictions to follow suit. Data such as these are essential in order to conduct research in field situations. Differences between samples collected near aquaculture sites and those collected from reference sites cannot be realistically interpreted or discussed, without knowledge of activities at those sites. Scotland reports full data sets from individual farms including biomass on site and data including quantities all compounds used at that site and when they were applied.

Table 7 is a summary of the quantities of therapeutants used in salmon aquaculture in Norway, Chile, Scotland and Canada in 2007.

Chemical use shown is relative to FAO-reported production value for Atlantic salmon only. We recognize that other salmon species are cultured in some jurisdictions and that therapeutants are applied to salmon during their first year in cages, i.e. to salmon that do not contribute to the production values.

Individual compounds have specific characteristics in terms of toxicity, modes of action and potential to affect marine environments. We also recognize that therapeutants have specific targets and dosage rates that may change according to environmental conditions. The antiparasitic products, for example, are much more lethal to most aquatic species than antibiotics. Excess use of antibiotics, however, may affect human health via promoting the development of antibiotic resistance in pathogens. Comparing quantities of antibiotics applied or rates of use to quantities or rates of use of antiparasitic is of no value. This table is of most value in comparing, between jurisdictions, the quantities of each class of product (antibiotic, antiparasitics, etc.). While the caveats mentioned above limit the ability to compare jurisdictions in an absolute way, we believe from the data available that the trends shown are an accurate reflection of the chemical use patterns in the aquaculture industry.

Table 7 shows that in 2007 the Chilean industry used antibiotics at a rate that is over 1400 times greater than in Norway (New York Times, 2008, 2009). In 2007 salmon farmers in Canada also treated fish with antibiotics at a significantly higher rate than reported in Norway and Scotland although the rate is about half that reported for Chile.

7. Research gaps

All jurisdictions require yearly reporting of the therapeutants used and the quantity applied. In Norway, Scotland and Canada these data can be accessed by the public with varying levels of ease. Data from

Table 6
Anaesthetics used in the Norwegian aquaculture industry and quantities used from 2003–2008. Source: Norwegian Institute of Public Health (2009) and Scottish Environmental Protection Agency.

Compound	Country	2006	2007	2008
Benzocaine	Norway	400	700	800
	Scotland	7.0	0	0
MS-222®	Norway	1248	1269	2132
	Scotland	41.8	60.1	48.5
Isoeugenol	Norway	6.5	5	25
2-propanone (L)	Scotland	120	0	0
Phenoxy ethanol (L)	Scotland	0	55	0

Table 7
Classes of chemical compounds used in Atlantic salmon aquaculture, quantities used in 2007 and quantities applied relative to production.

Country	Salmon production (metric ton)[a]	Therapeutant Type	kg (active ingredient) used	kg therapeutant/ metric ton produced
Norway	821,997	Antibiotics	649	0.0008
		Anti-louse	132	0.00016
Chile	330,791	Antibiotics	385,600	1.17
		Anti-louse	600.1	0.0018
UK	132,528	Antibiotics	1553	0.0117
		Anti-louse	194.8	0.0015
Canada (includes data from Maine, USA)	121,370[b]	Antibiotics	21,330[c]	0.175
		Anti-louse	19.8	0.00016

[a] Data accessed at FAO (April 2010) (http://www.fao.org/fi/website/FIRetrieveAction.do?dom=collection&xml=global-aquaculture-production.xml&xp_nav=1).
[b] Data accessed at http://www.dfo-mpo.gc.ca/communic/statistics/aqua/index_e.htm (October 2009) and New Brunswick Salmon Growers Association (personal communication 2009).
[c] Government of British Columbia (October 2009) (http://www.al.gov.bc.ca/ahc/fish_health/antibiotics.htm and New Brunswick Salmon Growers Association (personal communication).

Chile, until recently, was not available. The trend in Europe and Canada during the past decade has been towards a reduction in the quantity of antibiotics used although incidence of disease outbreak can lead to variability in quantities used. This year-to-year variability can, in all cases be traced to localized outbreaks of specific diseases which require antibiotic use. It is clear that the Chilean industry has, in the past applied quantities of antibiotics that are orders of magnitude larger than that applied in Europe. It is hoped that in the future data of antibiotic use will continue to be made available from the Chilean industry so that researchers and practicing veterinarians can identify trends, problems (if they exist) and mitigative responses. Similarly, data from Canadian farms is in many provinces not available. Fortunately summaries are available from the two largest producers of farmed salmon, New Brunswick and British Columbia.

Data generally suggest that negative impacts from anti-louse treatments, if they occur, are minor and will be restricted in spatial and temporal scale. However, published field data are rare. While drug manufacturers must provide extensive environmental monitoring data to regulators, most publicly available information regarding the biological effects of the various compounds is generated for single-species, lab-based bioassays which are unable to predict field effects. Significant quantities of antiparasitics were used in Chile in 2007 (Tables 3 and 7) and it is expected that there will be a significant increase in the use of antiparasitics reported in eastern Canada for 2009. In fact, many farms will have to treat more than the recommended three times during the production cycle in order to try to keep the sea lice infestations under control (M. Beattie, Province of New Brunswick, personal communication).

Farms are located in waters with different capacities to absorb wastes, including medicinal chemicals, without causing unacceptable environmental impacts. Risks therefore have a site-specific component, and management of these risks may therefore require site-specific assessments of the quantities of chemicals that can safely be used at each site. In the European Union, Maximum Residue Levels (MRL) are set for all therapeutants in food fish. Health Canada and the Canadian Food Inspection Agency have similar guidelines. In Scotland a medicine or chemical agent cannot be discharged from a fish farm unless formal consent under the Control of Pollution Act has been granted to the farm by SEPA. SEPA also requires annual reporting of therapeutant use from each site and these data are available to the public. This regulatory scheme provides an example of a risk management plan that should be adopted in all areas that use sea lice therapeutants.

No studies (lab or field) have adequately addressed cumulative effects. Salmon farms do not exist in isolation. Coincident treatments of parasiticides may have the benefit of reducing further infestation, therefore reducing the need to treat and the quantity of product applied. However coincident treatments may also affect salmon as well as non-target organisms. Multiple treatments within a single area may result if significantly different exposure regimes for non-targets organisms than a single treatment. While commercially important species such as lobsters have received a fair amount of research attention other marine invertebrates have not.

The authors recognize the site specificity associated with near-shore salmon aquaculture and that jurisdictional differences in the physical, chemical and regulatory environment may make it difficult to develop standard metrics for all areas where salmon aquaculture is practiced. In addition, we recognize that individual chemicals used in the salmon aquaculture industry are regulated to a significant extent in all jurisdictions. There are, however, a number of research questions which, once answered, may satisfy many of the concerns related to salmon aquaculture practices or to identify areas where current practices must be changed or mitigation measures initiated. Suggestions for further research are as follows:

Research into the fate and effects of compounds and mixtures from the “real world” must be pursued to provide data regarding cumulative effects and when coupled with data on the use of compounds, numbers of fish, etc. can result in realistic risk assessments. All therapeutants and antifouling agents, regardless of whether or not they are considered to contain biocides, should be tested for toxicity to different taxa of marine organisms.

Research is needed to determine the consequences of application of large quantities of antibiotics. The effects on fish (farmed and indigenous) health, human health and on the microflora and fauna in the sediments and the water column should be investigated. There is some discussion and contention regarding the occurrence of antibiotic application for prophylaxis. Should prophylactic use of antibiotics take place in any jurisdiction, this practice should cease. In addition, Classes of antibiotic compounds used for treatment of human diseases should not be used (or should be used with extreme reluctance) in aquaculture production of salmon.

Research is needed to develop more, or (preferably) alternative, products for sea lice control. With a limited number of treatment options, it is likely that resistance will develop in sea lice populations.

Research is needed to develop non-toxic forms of antifoulants. Research is needed to determine the biological effects on local organisms, either at individual or population level, of copper and zinc at concentrations above regulatory limits. Nets and cages should never be washed in the ocean or estuaries, where considerable amounts of toxic antifoulants could be released into the marine environment.

There are very few data available regarding the presence of disinfectants, and particularly of formulation products, in the marine environment. Studies need to document the patterns of use and the temporal and spatial scales over which compounds can be found.

There are very few data available regarding the use patterns of anaesthetics in salmon aquaculture. Collection and analysis of these data may help determine if more studies are required to determine if any products pose a risk to aquatic biota.

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References

Aarestrup, F.M., 2006. The origin, evolution, and local and global dissemination of antimicrobial resistance. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, DC, pp. 339–359.

Abele-Oeschger, D., Sartoris, F.J., Portner, H.O., 1997. Hydrogen peroxide causes a decrease in aerobic metabolic rate and in intracellular pH in the shrimp *Crangon crangon*. Comp. Biochem. Physiol. C 117 (2), 123–129.

Akinbowale, O.L., Peng, H., Grant, P., Darton, M.D., 2007. Antibiotic and heavy metal resistance in motile aeromonads and pseudomonads from rainbow trout (*Oncorhynchus mykiss*) farms in Australia. Int. J. Antimicrob. Agents 30, 177–182.

Alderman, D.J., Hastings, T.D., 1998. Antibiotic use in aquaculture: development of antibiotic resistance — potential for consumer health risks. Int. J. Food Sci. Technol. 33, 139–155.

Alekshun, M.N., Levy, S.B., 2007. Molecular mechanisms of antibacterial multidrug resistance. Cell 128, 1037–1050.

Alonso, A., Sánchez, P., Martínez, J.L., 2001. Environmental selection of antibiotic resistance genes. Environ. Microbiol. 3, 1–9.

Anderson, J.A., 1992. Allergic reactions to drugs and biological agents. J. Am. Med. Assoc. 268, 2844–2857.

Anderson, B.S., Hunt, J.W., Piekarski, W.J., Phillips, B.M., Englund, M.A., Tjeerdema, R.S., Goetzl, J.D., 1995. Influence of salinity on copper and azide toxicity to larval topsmelt *Atherinops affinis* (Ayres). Arch. Environ. Contam. Toxicol. 29, 366–372.

Angulo, F.J., 2000. Antimicrobial agents in aquaculture: potential impact on health. APUA Newslett. 18, 1–6.

Angulo, F.J., Baker, N.L., Olsen, S.J., Anderson, A., Barrett, T.J., 2004. Antimicrobial use in agriculture: controlling the transfer of antimicrobial resistance to humans. Sem. Pediat. Infect. Dis. 15, 78–85.

Arcangioli, M.-A., Leroy-Sétrin, S., Martel, J.-L., Chaslus-Dancla, E., 1999. A new chloramphenicol and florfenicol resistance gene flanked by two integron structures in *Salmonella typhimurium* DT104. FEMS Microbiol. Lett. 174, 327–332.
Armstrong, S.M., Hargrave, B.T., Haya, K., 2005. Antibiotic use in finfish aquaculture: modes of action, environmental fate and microbial resistance. In: Hargrave, B.T. (Ed.), Handbook of Environmental Chemistry, Vol 5 Part M, pp. 341–357.
Arnott, G.H., Ahsanullah, M., 1979. Acute toxicity of copper, cadmium and zinc to three species of marine copepods. Aust. J. Mar. Freshw. Res. 30, 63–71.
Austin, B., Austin, D.A. (Eds.), 1999. Bacterial Fish Pathogens. Disease of Farmed and Wild Fish, 3 rd Edition. Springer-Praxis Publishing, United Kingdom.
Baillie, A.C., 1985. The biochemical mode of action of insecticides. In: Jones, N.F. (Ed.), Recent Advances in the Chemistry of Insect Control: The Royal Society of Chemistry, Special Publication, 53, pp. 1–23.
Baquero, F., Martínez, J.-L., Cantón, R., 2008. Antibiotics and antibiotic resistance in water environments. Curr. Opin. Biotechnol. 19, 260–265.
Barton, B.A., Iwama, G.K., 1991. Physiological changes in fish from stress in aquaculture with emphasis on the response and effects of corticosteroids. Annu. Rev. Fish Dis. 1, 3–26.
Bechmann, R.K., 1994. Use of life tables and LC50 tests to evaluate chronic and acute toxicity effects of copper on the marine copepod *Tisbe furcata* (Baird). Environ. Toxicol. Chem. 13, 1509–1517.
Bellas, J., 2005. Toxicity assessment of the antifouling compound zinc pyrithione using early developmental stages of the ascidian *Ciona intestinalis*. Biofouling 21, 289–296.
Bellas, J., Vasquez, E., Beiras, R., 2001. Toxicity of Hg, Cu, Cd, and Cr on early developmental stages of *Ciona intestinalis* (Chordata, Ascidiacea) with potential application in marine water quality assessment. Water Res. 35, 2905–2912.
Beveridge, M., 2004. Cage Aquaculture, 3 rd. Edition. Blackwell Publishing, Ames. Iowa.
Borgmann, U., Norwood, W.P., Clarke, C., 1993. Accumulation, regulation and toxicity of copper, zinc, lead, and mercury in *Hyalella azteca*. Hydrobiologia 259, 79–89.
Boxall, A.B., Fogg, L.A., Blackwell, P.A., Kay, P., Pemberton, E.J., Croxford, A., 2004. Veterinary medicines in the environment. Rev. Environ. Contam. Toxicol. 180, 1–91.
Braithwaite, R.A., Carracosa, M.C., McEvoy, L.A., 2006. Biofouling of salmon cage netting and the efficacy of a typical copper-based antifoulant. Aquaculture 262, 219–226.
Branson, E.J., Diaz-Munoz, D., 1991. Description of a new disease condition occurring in farmed coho salmon, *Oncorhynchus kisutch* (Walbaum), in South America. J. Fish Dis. 14, 147–156.
Branson, E.J., Ronsberg, S.S., Ritchie, G., 2000. Efficacy of teflubenzuron (Calicide®) for the treatment of sea lice, *Lepeophtheirus salmonis* (Krøyer 1838), infestations of farmed Atlantic salmon (*Salmo salar* L.). Aquac. Res 31, 861–867.
Bravo, S., 2009. The sea lice situation in Chile. World Aquac. 40 (2), 26–28.
Bravo, S., Midtlyng, P.J., 2007. The use of vaccines in the Chilean salmon industry 1999–2003. Aquaculture 270, 36–42.
Bravo, S., Dolz, H., Silva, M.T., Lagos, C., Millanao, A., Urbina, M. 2005. Informe Final. Diagnostico del uso de fármacos y otros productos químicos en la acuicultura. Universidad Austral de Chile. Facultad de Pesquerias y Oceansgrafia, Instituto de Acuicultura. Casilla 1327. Puerto Montt, Chile. Proyecto No. 2003–28.
Bravo, S., Sevatdal, S., Horsberg, T.E., 2008. Sensivity assessment of Caligus rogercresseyi to emamectin benzoate in Chile. Aquaculture 282, 7–12.
Briggs, C.E., Fratamico, P.M., 1999. Molecular characterization of an antibiotic resistance gene cluster of *Salmonella typhimurium* DT104. Antimicrob. Agents Chemother. 43, 846–849.
Brocklebank, J.R., Evelyn, T.P.T., Speare, D.J., Armstrong, R.D., 1993. Ricketsial septicemia in farmed Atlantic and Chinook salmon in British Columbia: clinical presentation and experimental transmission. Can. Vet. J. 34, 745–748.
Brooks, K.M., 2000. Determination of copper loss rates from Flexgard XI™ treated nets in marine environments and evaluation of the resulting environmental risks. Report to the Ministry of Environment for the BC Salmon Farmers Association, 1200 West Pender St. Vancouver BC. 24 pp.
Brooks, K.M., Mahnken, C.V., 2003. Interactions of Atlantic salmon in the Pacific Northwest environment III Accumulation of zinc and copper. Fish. Res. 62, 295–305.
Brooks, K.M., Mahnken, C., Nash, C., 2002. Environmental effects associated with marine net pen waste, with emphasis on salmon farming in the Pacific Northwest. In: Stickney, R., McVey, J. (Eds.), Responsible Marine Aquaculture. World Aquaculture Society, pp. 159–204.
Brooks, K.M., Stierns, A.R., Mahnken, C.V., Blackburn, D.B., 2003. Chemical and biological remediation of the benthos near Atlantic salmon farms. Aquaculture 219, 355–377.
Bruno, D.W., Raynard, R.S., 1994. Studies on the use of hydrogen peroxide as a method for the control of sea lice on Atlantic salmon. Aquac. Int. 2, 10–18.
Burridge, L.E., 2003. Chemical use in marine finfish aquaculture in Canada: a review of current practices and possible environmental effects. Can. Tech. Rep. Fish. Aquat. Sci. 2450 [ix + 131 pp.].
Burridge, L.E., Chou, C.L. 2005. Copper in Atlantic salmon tissues collected from Heritage Salmon hatchery and net pen operations. Unpublished paper. 6 pp.
Burridge, L.E., Haya, K., 1997. The Lethality of pyrethrins to larvae and post-larvae of the American lobster (*Homarus americanus*). Ecotoxicol. Environ. Saf. 38 (2), 150–154.
Burridge, L.E., Zitko, V., 2002. Lethality of copper sulfate and copper-treated nets to juvenile haddock, *Melanogrammus aeglefinus* L. Bull. Environ. Contam. Toxicol. 69, 378–383.
Burridge, L.E., Doe, K., Haya, K., Jackman, P.M., Lindsay, G., Zitko, V., 1999. Chemical analysis and toxicity tests on sediments under salmon net pens in the Bay of Fundy. Can. Tech. Rep. Fish. Aquat. Sci., 2291. iii + 39 pp.
Burridge, L.E., Haya, K., Waddy, S.L., Wade, J., 2000a. The lethality of anti-sea lice formulations Salmosan® (Azamethiphos) and Excis® (Cypermethrin) to stage IV and adult lobsters (*Homarus americanus*) during repeated short-term exposures. Aquaculture 182 (1–2), 27–35.
Burridge, L.E., Haya, K., Page, F., Waddy, S.L., Zitko, V., Wade, J., 2000b. The lethality of the cypermethrin formulation Excis® to larval and post-larval stages of the American lobster (*Homarus americanus*). Aquaculture 182 (1–2), 37–47.
Burridge, L.E., Hamilton, M.N., Waddy, S.L., Haya, K., Mercer, S.M., Greenhalgh, R., Tauber, R., Radecki, S.V., Crouch, L.S., Wislocki, P.G., Endris, R.G., 2004. Acute toxicity of emamectin benzoate in fish feed to American lobster, *Homarus americanus*. Aquac. Res. 35 (8), 713–722.
Burridge, L.E., Haya, K., Waddy, S.L., 2008. The effect of repeated exposure to the organophosphate pesticide, azamethiphos, on survival and spawning in female American lobsters (*Homarus americanus*). Ecotoxicol. Environ. Saf., 69, pp. 411–415.
Buschmann, A.H., Riquelme, V.A., Hernández-González, M.C., Varela, D., Jiménez, J.E., Henríquez, L.A., Vergara, P.A., Guíñez, R., Filún, L., 2006. A review of the impacts of salmon farming on marine coastal ecosystems in the southeast Pacific. ICES J. Mar. Sci. 63, 1338–1345.
Cabello, F.C., 2003. Antibiotics and aquaculture. An analysis of their potential impact upon the environment, human and animal health in Chile.Fundacion Terram. Analisis de Politicas Publicas, No. 17, pp. 1–16 (www.terram.cl/index).
Cabello, F.C., 2004. Antibiotics and aquaculture in Chile: implications for human and animal health. Rev. Med. Chile 132, 1001–1006.
Cabello, F.C., 2006. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. Environ. Microbiol. 8, 1137–1144.
Campbell, W.C., 1989. Ivermectin and Abamectin. Springer Verlag, New York.
Capone, D.G., Weston, D.P., Miller, V., Shoemaker, C., 1996. Antibacterial residues in marine sediments and invertebrates following chemotherapy in aquaculture. Aquaculture 145, 55–75.
Cattoir, V., Poirel, L., Mazel, D., Soussy, C.-J., Nordmann, P., 2007. *Vibrio splendidus* as the source of plasmid-mediated QnrS-like quinolone resistance determinants. Antimicrob. Agents Chemother. 51, 2650–2651.
Cattoir, V., Poirel, L., Aubert, C., Soussy, C.-J., Nordmann, P., 2008. Unexpected occurrence of plasmid-mediated quinolone resistance determinants in environmental *Aeromonas* spp. Emerg. Infect. Dis. 14, 231–237.
Ceccarelli, D., Salvia, A.M., Sami, J., Cappuccinelli, P., Colombo, M.M., 2006. New cluster of plasmid-located class 1 integrons in *Vibrio cholerae* O1 and a *dfrA15* cassette-containing integron in *Vibrio parahaemolyticus* isolated in Angola. Antimicrob. Agents Chemother. 50, 2493–2499.
Cerniglia, C.E., Kotarski, S., 2005. Approaches and safety evaluations of veterinary antimicrobial agents in food to determine the effects on human intestinal microflora. J. Vet. Pharmacol. Ther. 28, 3–20.
Chou, C.L., 2007. A time series of mercury accumulation and improvement of dietary feed in net caged Atlantic salmon (*Salmo salar*). Mar. Poll. Bull. 54, 720–725.
Chou, C.L., Haya, K., Paon, L.A., Burridge, L., Moffatt, J.D., 2002. Aquaculture-related trace metals in sediments and lobsters and relevance to environmental monitoring program ratings for near-field effects. Mar. Poll. Bull. 44, 1259–1268.
Christensen, A.M., Ingerslev, F., Baun, A., 2006. Ecotoxicity of mixtures of antibiotics used in aquacultures. Environ. Toxicol. Chem. 25, 2208–2215.
Cid, A., Herrero, C., Torres, E., Abalde, J., 1995. Copper toxicity on the marine microalga *Phaeodactylum tricornutum*: effects on photosynthesis and related parameters. Aquat. Toxicol. 31, 165–174.
Clark, J.R., Patrick Jr., J.M., Moore, J.C., Lores, E.M., 1987. Waterborne and sediment-source toxicities of six organic chemicals to grass shrimp (*Palaemonetes pugio*) and amphioxus (*Branchiostoma caribaeum*). Arch. Environ. Contam. Toxicol. Vol. 16 (4), 401–407.
Coglianese, M.P., Martin, M., 1981. Individual and interactive effects of environmental stress on the embryonic development of the Pacific oyster *Crassostrea gigas*. I: the toxicity of copper and silver. Mar. Environ. Res. 5, 13–27.
Cosgrove, S.E., Saye, K.S., Eliopoulos, G.M., Carmeli, Y., 2002. Health and economic outcomes of the emergence of third generation cephalosporin resistance in Enterobacter species. Arch. Intern. Med. 162, 185–190.
Costello, M.J., Grant, A., Davies, I.M., Cecchini, S., Papoutsoglou, S., Quigley, D., Saroglia, M., 2001. The control of chemicals used in aquaculture in Europe. J. Appl. Ichthyol. 17, 173–180.
Cotran, R.S., Kumar, V., Robbins, S.L., 1989. Pathological Basis of Disease, 4 ed. Saunders, Toronto.
Coyne, R., Hiney, M., Smith, P., 1997. Transient presence of oxytetracycline in blue mussels (*Mytilus edulis*) following its therapeutic use at a marine Atlantic salmon farm. Aquaculture 149, 175–181.
Dauer, D.M., Rodi, A.J., Ranasingh, A., 1992. Effects of low dissolved oxygen events on the macrobenthos of the lower Chesapeake Bay. Estuaries 15, 384–391.
Davenport, J., Back, K., Burnell, G., Cross, T., Culloty, S., Ekaratne, S., Furness, B., Mulcahy, M., Thetmeyer, H., 2003. Aquaculture. The Ecological Issues. Blackwell Science Ltd, Berlin, Germany.
Davis, J.H., 1985. The pyrethroids: an historical introduction. In: Leahey, J.P. (Ed.), The Pyrethroid Insecticides. Taylor and Francis Ltd., London, pp. 1–41.
Dean, R.J., Shimmield, T.M., Black, K.D., 2007. Copper, zinc and cadmium in marine cage fish farm sediments: an extensive survey. Environ. Pollut. 145, 84–95.
Debourg, C., Johnson, A., Lye, C., Tornqvist, L., Unger, C., 1993. Antifouling products pleasure boats, commencial vessels, net, fish cages, and other underwater equipment. KEM Report, No 2/93. The Swedish National Chemicals Inspectorate. 58 pp.
DeBruyn, A., Trudel, M., Eyding, N., Harding, J., McNally, H., Mountain, R., Orr, C., Urban, D., Verenitch, S., Mazumder, A., 2006. Ecosystemic effects of salmon farming increase mercury contamination in wild fish. Environ. Sci. Technol. 40 (11), 3489–3493.
Doublet, B., Schwarz, S., Kehrenberg, C., Cloeckaert, A., 2005. Florfenicol resistance gene *floR* is part of a novel transposon. Antimicrob. Agents Chemother. 49, 2106–2108.
Eisler, R., 1992. Diflubenzuron hazards to fish, wildlife, and invertebrates: a synoptic review. US Fish and Wildlife Service. Contam. Hazard Rev. 25, 4 36 pp.

Ernst, W., Jackman, P., Doe, K., Page, F., Julien, G., Mackay, K., Sutherland, T., 2001. Dispersion and toxicity to non-target aquatic organisms of pesticides used to treat sea lice on salmon in net pen enclosures. Mar. Poll. Bull. 42, 433–444.
FAO: Food and Agriculture Organization of the United Nations 2010. www.fao.org/fishery/aquaculture/en. Accessed April 13, 2010.
Finlayson, B.J., Verrue, K.M., 1982. Toxicity of copper, zinc and cadmium mixtures to juvenile chinook salmon. Trans. Am. Fish. Soc. 111, 645–650.
Fischer, S.A., Hall, L.W., 1992. Environmental concentrations and aquatic toxicity data on diflubenzuron (Dimilin). Crit. Rev. Toxicol. 22, 45–79.
Fish Farming Expert. 2008. www.fishfarmingxpertno/index.php?page_id=37&article_id=78056. Accessed April, 30, 2010.
Fortt, Z.A., Cabello, F.C., Buschmann, R.A., 2007. Residues of tetracycline and quinolones in wild fish living around a salmon aquaculture center in Chile. Rev. Chil. Infect. 24, 14–18.
Franklin, N.M., Stauber, J., Lim, R., 2001. Development of flow cytometry-based algal bioassays for assessing toxicity of copper in natural waters. Environ. Toxicol. Chem. 20, 160–170.
Furushita, M., Shiga, T., Maeda, T., Yahata, M., Kaneoka, A., Takahashi, Y., Torii, K., Hasegawa, T., Ohta, M., 2003. Similarity of tetracycline resistance genes isolated from fish farm bacteria to those from clinical isolates. Appl. Environ. Microbiol. 69, 5336–5342.
Garnacho, E., Peck, L.S., Tyler, P.A., 2000. Variations between winter and summer in the toxicity of copper to a population of the mysid *Praunus flexuosus*. Mar. Biol. 137, 631–636.
GESAMP, 1997. Towards safe and effective use of chemicals in coastal aquaculture. GESAMP Reports and Studies No. 65 Publ. IMO/FAO/UNESCO/IOC/WMO/WHO/IAEA/UN/UNEP., FAO Rome Italy 40 pp.
Godoy, M.G., Aedo, A., Kibenge, M.J., Groman, D.B., Yason, C.V., Grothusen, H., Lisperguer, A., Calbucura, M., Avendaño, F., Imilán, M., Jarpa, M., Kibenge, F.S., 2008. First detection, isolation and molecular characterization of infectious salmon anaemia virus association with clinical disease in farmed Atlantic salmon (*Salmo salar*) in Chile. BMC Vet. Res. 4, 28.
Gonçalves Ferreira, C.S., Nunes, B.A., de Melo Henriques-Almeida, J.M., Guilhermino, L., 2007. Acute toxicity of oxytetracycline and florfenicol to the microalgae *Tetraselmis chuii* and to the chrustacean *Artemia parthenogenetica*. Acotoxicol. Environ. Saf. 67, 452–458.
Grant, A.N., 2002. Medicines for sea lice. Pest. Manag. Sci. 58, 521–527.
Grave, K., Markestad, A., Bangen, M., 1996. Comparison in prescribing patterns of antibacterial drugs in salmonid farming in Norway during the periods 1980–1988 and 1989–1994. J. Vet. Pharmacol. Ther. 19, 184–191.
Grave, K., Lingaas, E., Bangen, M., Rønning, R.M., 1999. Surveillance of the overall consumption of antibacterial drugs in humans, domestic animals and farmed fish in Norway in 1992 and 1996. J. Antimicrob. Chemother. 43, 243–252.
Guardabassi, L., Courvalin, P., 2006. Modes of antimicrobial action and mechanisms of bacterial resistance. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, D.C., pp. 1–18.
Hansen, J.I., Mustafa, T., Depledge, M., 1992. Mechanisms of copper toxicity in the shore crab, *Carcinus maenas*. Mar. Biol. 114, 259–264.
Harmon, V.L., Langdon, C.J., 1996. A 7-day toxicity test for marine pollutants using the Pacific mysid *Mysidopsis intii*. 2. Protocol evaluation. Environ. Toxicol. Chem. 15, 1824–1830.
Hastings, P.J., Rosenberg, S.M., Slack, A., 2004. Antibiotic-induced lateral transfer of antibiotic resistance. Trends Microbiol. 12, 401–404.
Hawkey, P.M., 2008. The growing burden of antimicrobial resistance. J. Antimicrob. Chemother. 62 (Suppl. 1), i1–i9. doi:10.1093/jac/dkn241.
Haya, K., Burridge, L.E., Davies, I.M., Ervik, A., 2005. A review and assessment of environmental risk of chemicals used for the treatment of sea lice infestations of cultured salmon. In: Hargrave, B. (Ed.), Handbook of Environmental Chemistry: Water Pollution, Part M, Volume 5, pp. 305–341.
Health Canada 2010. Register of innovative drugs. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/regist/reg_innov_dr-eng.php. Accessed April 2010.
Hektoen, H., Berge, J.A., Hormazabal, V., Yndestad, M., 1995. Persistence of antibacterial agents in marine sediments. Aquaculture 133, 175–184.
Herkovitz, J., Helguero, L.A., 1998. Copper toxicity and copper-zinc interactions in amphibian embryos. Sci. Total Environ. 221, 1–10.
Heuer, O.E., Kruse, H., Grave, K., Collignon, P., Karunasagar, I., Angulo, F.J., 2009. Human health consequences of use of antimicrobial agents in aquaculture. Clin. Infect. Dis. 49, 1248–1253.
Holten Lützhøft, H.-C., Halling-Sørensen, B., Jørgensen, S.E., 1999. Algal toxicity of antibacterial agents applied in Danish fish farming. Arch. Environ. Contam. Toxicol. 36, 1–6.
Hornberger, M.I., Luoma, S.N., Cain, D.J., Parchaso, F., Brown, C.L., Bouse, R.M., Wellise, C., Thompson, J.K., 2000. Linkage of bioaccumulation and biological effects to changes in pollutant loads in south San Francisco Bay. Environ. Sci. Technol. 34, 2401–2409.
Hunter, R.P., Fraser, N., 1995. Field monitoring of the effects of cypermethrin as GPRD01. Report of Grampian Pharmaceuticals Limited, Research Division. Ref GP95033.
Jacoby, G.A., Gacharna, N., Black, T.A., Miller, G.H., Hooper, D.C., 2009. Temporal appearance of plasmid-mediated quinolone resistance genes. Antimicrob. Agents Chemother. 53, 1665–1666.
Jensen, N.R., Collins, K.C., 2003. Time required for yolk coagulation in pink salmon and steelhead eggs exposed to mechanical shock. North Am. J. Aquacul. 65, 330–338.
Johnson, S.C., Treasurer, J.W., Bravo, S., Nagasawa, K., Kabata, Z., 2004. A review of the impact copepods on marine aquaculture. Zool. Stud. 43, 229–243.
Jones, M.W., Sommerville, C., Wootten, R., 1992. Reduced sensitivity of the salmon louse, *Lepeophtheirus salmonis*, to the organophosphate dichlorvos. J. Fish Dis. 15, 197–202.
Kahn, N.Y., 1983. In: Miyamoto, J., Kearney, P.C. (Eds.), Pesticide chemistry: human welfare and the environment. Proceedings of the Fifth International Congress of Pesticide Chemistry, Kyoto, Japan, 1982. Permagon Press, Oxford, pp. 437–450.
Karakassis, I., Tsapakis, M., Hatziyanni, E., 1998. Seasonal variability in sediment profiles beneath fish farm cages in the Mediterranean. Mar. Ecol. Prog. Ser. 162, 243–252.
Kibenge, F.S., Godoy, M.G., Wang, Y., Libenge, M.J., Gherardelli, V., Mansilla, S., Lisperger, A., Jarpa, M., Larroquete, G., Avendaño, F., Lara, M., Gallardo, A., 2009. Infectious salmon anaemia virus (ISAV) isolated from the ISA disease outbreaks in Chile diverged from ISAV isolates from Norway around 1996 and was disseminated around 2005, based on surface glycoprotein gene sequences. Virol. J. 6, 88.
Kiemer, M.C.B., Black, K.D., 1997. Effects of hydrogen peroxide on gill tissues of Atlantic salmon, *Salmo salar* L. Aquaculture 153, 181–189.
Kim, E.-H., Aoki, T., 1996. Sulfonamide resistance gene in a transferable R plasmid of *Pasteurella piscicida*. Microbiol. Immunol. 40, 397–399.
King, C.K., 2001. Effects of metal contaminants on the development of the common Antarctic sea urchin *Sterechinus neumayeri* and comparisons of sensitivity with tropical and temperate echinoids. Mar. Ecol. Prog. Ser. 215, 143–154.
Klerks, P., Weis, J.S., 1987. Genetic adaptation to heavy metals in aquatic organisms: a review. Environ. Pollut. 45, 173–206.
Lang, W.H., Forward, R.B., Miller, D.C., Marcy, M., 1980. Acute toxicity and sublethal behavioral effects of copper on barnacle nauplii (*Balanus improvisus*). Mar. Biol. 58, 139–145.
Le Jeune, A.H., Charpin, M., Briand, J.F., Lenain, J.F., Baudu, M., Amblard, C., 2006. Effect of copper sulphate treatment on natural phytoplanktonic communities. Aquat. Toxicol. 80, 267–280.
Lees, F., Baillie, M., Gettinby, G., Revie, C.W. 2008. The efficacy of emamectin benzoate against infestations of *Lepeophtheirus salmonis* on farmed Atlantic salmon (*Salmo salar* L) in Scotland, 2002–2006. Open Access article published on line: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001549. Accessed Feb 22, 2008.
Levy, S.B., 2001. Antibiotic resistance: consequences of inaction. Clin. Infect. Dis. 33 (Suppl. 3), S124–S129.
Levy, S.B., 2002. Factors impacting on the problem of antibiotic resistance. J. Antimicrob. Chemother. 49, 25–30.
Lewis, A.G., Metaxas, A., 1991. Concentrations of total dissolved copper in and near a copper-treated salmon net pen. Aquaculture 99, 267–276.
Lillehaug, A., Lunestad, B.T., Grave, K., 2003. Epidemiology of bacterial diseases in Norwegian aquaculture — a description based on antibiotic prescription data for the ten-year period 1991 to 2000. Dis. Aquat. Org. 53, 115–125.
Linssen, M.R., van Aggelen, G.C., Endris, R., 2002. Toxicity of emamectin benzoate in fish feed to adults of the spot prawn and dungeness crab. In: Eichkoff, C.V., van Aggelen, G.C., Niimi, A. (Eds.), Proceedings of the 29th Annual Aquatic Toxicity Workshop: Oct. 21–23, 2002, Whistler, British Columbia: Canadian Technical Report of Fisheries and Aquatic Sciences, 2438 (abstract).
Lorentzen, M., Maage, A., 1999. Trace element status of juvenile Atlantic salmon *Salmo salar* L. fed a fish-meal based diet with or without supplementation of zinc, iron, manganese, and copper from first feeding. Aquacult. Nutr. 5, 163–171.
MacGowan, A.P., on behalf of the BSAC Working Parties on Resistance surveillance, 2008. Clinical implications of antimicrobial resistance for therapy. J. Antimicrob. Chemother. 62 (Suppl. 2) ii105–ii114.
Maragakis, L.L., Perencevich, E.N., Cosgrove, S.E., 2008. Clinical and economic burden of antimicrobial resistance. Expert Rev. Anti Infect. Ther. 6, 751–763.
Markestad, A., Grave, K., 1997. Reduction of antibacterial drug use in Norwegian fish farming due to vaccination. Fish Vaccinol. 90, 365–369.
Martinez, J.L., 2009. The role of natural environments in the evolution of resistance traits in pathogenic bacteria. Proc. R. Soc. B 276, 2521–2530.
Mauel, M.J., Miller, D.L., 2002. Piscirickettsiosis and piscirickettsiosis-like infections in fish: a review. Vet. Microbiol. 87, 279–289.
Mauel, M.J., Ware, C., Smith, P.A., 2008. Culture of *Piscirickettsia salmonis* on enriched blood agar. J. Vet. Diagn. Invest. 20, 213–214.
McIntosh, D., Cunningham, M., Ji, B., Fekete, F.A., Parry, E.M., Clark, S.E., Zalinger, Z.B., Gilg, I.C., Russell Danner, G., Johnson, K.A., Beattie, M., Ritchie, R., 2008. Transferable, multiple antibiotic and mercury resistance in Atlantic Canadian isolates of *Aeromonas salmonicida* subsp. *salmonicida* is associated with carriage of an IncA/C plasmid similar to the *Salmonella enterica* plasmid pSN254. J. Antimicrob. Chemother. 61, 1221–1228.
McLeese, D.W., Mecalfe, C.D., Zitko, V., 1980. Lethality of permethrin, cypermethrin and fenvalerate to salmon, lobster and shrimp. Bull. Environ. Contam. Toxicol. 25, 950–955.
Medina, M., Barata, C., Telfer, T., Baird, T.J., 2004. Effects of cypermethrin on marine plankton communities: a simulated field study using mesocosms. Ecotox. Environ. Saf. 58 (2), 236–245.
Mikalsen, J., Skjaervik, O., Wiik-Nielsen, J., Wasmuth, M.A., Colquhoun, D.J., 2008. Agar culture of *Piscirickettsia salmonis*, a serious pathogen of farmed salmonid and marine fish. FEMS Microbiol. Lett. 278, 43–47 Electronic publication 2007 Nov. 19.
Miller, T.A., Adams, M.E., 1982. Mode of action of pyrethroids. In: Coats, J.R. (Ed.), Insecticide Mode of Action. Academic Press, New York, pp. 3–27.
Miller, C.J., Rose, A.L., Waite, T.D., 2009. Impact of natural organic matter on H2O2-mediated oxidation of Fe(II) in a simulated freshwater system. Geochim. Cosmochim. Acta 73, 2758–2768.
Ministerio de Economia de Chile. 2009. Letter to Oceana on the use of antibiotics in salmon aquaculture. July 14.
Miranda, C.D., Rojas, R., 2007. Occurrence of florfenicol resistance in bacteria associated with two Chilean salmon farms with different history of antibacterial usage. Aquaculture 266, 39–46.
Miranda, C.D., Kehrenberg, C., Ulep, C., Schwarz, S., Roberts, M.C., 2003. Diversity of tetracycline resistance genes in bacteria from Chilean salmon farms. Antimicrob Agents Chemother. 47, 883–888.

Mitchell, A.J., Collins, C., 1997. Review of therapeutant use of hydrogen peroxide in fish production. Aquac. Mag. 23 (3), 74–79.

Mølbak, K., 2006. The clinical importance of animal-related resistance. Sørum H. Antimicrobial drug resistance in fish pathogens. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, DC, pp. 329–337.

Morris Jr., J.G., 1999. Harmful algal blooms: an emerging public health program with possible links to human stress on the environment. Annu. Rev. Energy Environ. 24, 367–390.

Morrisey, D.J., Gibbs, M.M., Pickmere, S.E., Cole, R.G., 2000. Predicting impacts and recovery of marine-farm sites in Stewart Island, New Zealand, from the Findlay–Watling model. Aquaculture 185, 257–271.

Nash, C.E. 2001 (editor) The Net Pen Salmon Farming Industry in the Pacific Northwest. U.S. Dept. of Commerce, NOAA Tech. Memo. NMFS – NWFSC-49. 125 pp.

Nash, C.E., 2003. Interactions of Atlantic salmon in the Pacific northwest VI. A synopsis of the risk and uncertainty. Fish. Res. 62, 339–347.

New York Times. 2007. F.D.A. curbs sales of five seafoods farmed in China. June 29.

New York Times. 2007a. China seafood industry: Dirty water, dangerous fish. December 15.

New York Times. 2008. Salmon virus indicts Chile's fishing methods. March 27.

New York Times. 2009. Chile's antibiotic use on salmon farms dwarfs top rival's. July 27.

Newman, M.C., Unger, M.A.2003. Fundamentals of Ecotoxicology. Lewis Publishers, CRC Press, Boca Raton FL 458 pp.

Nikaido, H., 2009. Multidrug resistance in bacteria. Annu. Rev. Biochem. 78 8.1–8.28.

Norwegian Institute of Public Health 2009. Pharmaceutical use in Norwegian fish farming in 2001–2008. Electronic citation Accessed August 2009: (http://www.fhi.no/eway/default.aspx?pid=233&trg=Area_5774&MainLeft_5669=5774:0:&Area_5774=5544:73848::0:5776:1:::0:0).

Olsen, A.B., Melby, H.P., Speilberg, L., Evensen, O., 1997. *Piscirickettsia salmonis* infection in Atlantic salmon *Salmo salar* in Norway — epidemiological, pathological and microbiological findings. Dis. Aquat. Org. 31, 35–48.

Osorio, C.R., Marrero, J., Wozniak, R.A.F., Lemos, M.L., Burrus, V., Waldor, M.K., 2008. Genomic and functional analysis of ICE*Pda*Spa1, a fish-pathogen-derived SXT-related integrating conjugative element that can mobilize a virulence plasmid. J. Bacteriol. 190, 3353–3361.

Page, F.H., Losier, R., McCurdy, P., Greenberg, D., Chaffey, J., Chang, B., 2005. Dissolved oxygen and salmon cage culture in the southwestern New Brunswick portion of the Bay of Fundy. In: Hargrave, B.T. (Ed.), The Handbook of Environmental Chemistry 5-M: Water Pollution Environmental Effects of Marine Finfish Aquaculture. Springer-Verlag, Berlin, pp. 1–28.

Pahl, B.C., Opitz, H.M., 1999. The effects of cypermethrin (Excis) and azamethiphos (Salmosan) on lobster, *Homarus americanus* H. Milne Edwards, larvae in a laboratory study. Aquac. Res. 30, 655–665.

Parker, W.R., Aube, J.G., 2002. Metal levels in sediment samples collected under salmon aquaculture pens in the Bay of Fundy, New Brunswick. Environment Canada, Environmental Protection Branch, Atlantic Region Surveillance Report. EPS-5-AR-02-01 30 pp.

Parker, W.R., Doe, K.G., Jackman, P., Aube, J.G., 2003. Toxicity of copper-based antifouling coatings to the marine amphipod, *Eohaustorius estuaries*. Environment Canada, Environmental Protection Branch, Atlantic Region Surveillance Report. EPS-5-AR-03-01 19 pp.

Perez, B.A., Albert, A.A., Contreras, J.R., Smith, P.A., 1998. Detection of *Piscirickettsia salmonis* in up-stream-migrating coho salmon, *Oncorhynchus kisutch*, in Chile. Bull. Eur. Assoc. Fish Pathol. 18, 189–191.

Peterson, L.K., D'Auria, J.M., McKeown, B.A., Moore, K., Shum, M., 1991. Copper levels in the muscle and liver tissue of farmed chinook salmon, *Oncorhynchus tshawytscha*. Aquaculture 99, 105–115.

Phelps, H.L., Hardy, J.T., Pearson, W.H., Apts, C.W., 1983. Clam burrowing behaviour: inhibition by copper-enriched sediment. Mar. Pollut. Bull. 14, 452–455.

Pike, A.W., 1989. Sea lice — major pathogens of farmed Atlantic salmon. Parasitol. Today 5, 291–297.

Pillay, T.V.R., 2004. Aquaculture and the Environment, 2nd Edition. Blackwell Publishing Ltd., United Kingdom.

Poirel, L., Liard, A., Rodriguez-Martinez, J.M., Nordmann, P., 2005a. Vibrionaceae as a possible source of Qnr-like quinolone resistance determinants. J. Antimicrob. Chemother. 56, 1118–1121 Electronic publication 2005 Oct 14.

Poirel, L., Rodriguez-Martinez, J.-M., Mammeri, H., Liard, A., Nordmann, P., 2005b. Origin of plasmid-mediated quinolone resistance determinant QnrA. Antimicrob. Agents Chemother. 49, 3523–3525.

Powell, D.P., 2000. Common fish diseases. In: Ostrander, G.K. (Ed.), The Laboratory Fish. Academic Press, New York, NY. Chapter 4.

Prescott, J.F., 2006. History of antimicrobial usage in agriculture: on overview. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, D.C, pp. 19–27.

Rach, J.J., Gaikowski, M.P., Ramsay, R.T., 2000. Efficacy of hydrogen peroxide to control parasitic infestations on hatchery-reared fish. J. Aquat. Animal Health 12, 267–273.

Reeve, M.R., Walter, M.A., Darcy, K., Ikeda, T., 1977. Evaluation of potential indicators of sub-lethal toxic stress in marine zooplankton (feeding, fecundity, respiration and excretion): controlled ecosystem pollution experiment. Bull. Mar. Sci. 27, 103–113.

Reid, H.I., Griffen, A.A., Birkbeck, T.H., 2004. Isolates of *Piscirickettsia salmonis* from Scotland and Ireland show evidence of clonal diversity. Appl. Environ. Microbiol. 70, 4393–4397.

Rhodes, G., Huys, G., Swings, J., Mc Gann, P., Hiney, M., Smith, P., Pickup, R.W., 2000. Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: implication of Tn1721 in dissemination of the tetracycline resistance determinant Tet A. Appl. Environ. Microbiol. 66, 3883–3890.

Richard, L.E., Peake, B.M., Rusak, S.A., Cooper, W.J., Burrit, D.J., 2007. Production and decomposition dynamics of hydrogen peroxide in freshwater. Environ. Chem. 4, 49–54.

Roberts, M.C., 2009. The evolution of antibiotic-resistant microbes in foods and host ecosystems. In: Jaykus, L.-A., Wang, H.H., Schlesinger, L.S. (Eds.), Food-Borne Microbes. Shaping the Host Ecosystem. ASM Press, Washington, D.C, pp. 213–229.

Roper, D.S., Hickey, C.W., 1994. Behavioural responses of the marine bivalve *Macomona liliana* exposed to copper- and chlordane-dosed sediments. Mar. Biol. 118, 673–680.

Roth, M., Richards, R.H., Sommerville, C., 1993. Current practices in the chemotherapeutic control of sea lice infestations in aquaculture: a review. J. Fish Dis. 16, 1–26.

Roth, M., Richards, R.H., Dobson, D.P., Rae, G.H., 1996. Field trials on the efficacy of the organophosphorus compound azamethipos for the control of sea lice (Copepoda: Caligidae) infestations of farmed Atlantic salmon (*Salmo salar*). Aquaculture 140, 217–239.

Roy, W.J., Sutherland, I.H., Rodger, H.D.M., Varma, K.J., 2000. Tolerance of Atlantic salmon, *Salmo salar* L. and rainbow trout, *Oncorhynchus mykiss* (Walbaum), to emamectin benzoate, a new orally administered treatment for sea lice. Aquaculture 184, 19–29.

Salyers, A.A., Gupta, A., Wang, Y., 2004. Human intestinal bacteria as reservoirs for antibiotic resistance genes. Trends Microbiol. 12, 412–416.

Samuelsen, O.B., Lunestad, B.T., Husev g, B., Hølleland, T., Ervik, A., 1992. Residues of oxolinic acid in wild fauna following medication in fish farms. Dis. Aquatic Org. 12, 111–119.

Sapkota, A., Sapkota, A.R., Kucharski, M., Burke, J., McKenzie, S., Walker, P., Lawrence, R., 2008. Aquaculture practices and potential human health risks: current knowledge and future priorities. Environ. Int. 24, 1215–1226.

Sarmah, A.K., Meyer, M.T., Boxal, A.B., 2006. A global perspective on the use, sales, exposure pathways, occurrence, fat and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 65, 725–759.

Schwarz, S., Cloeckaert, A., Roberts, M.C., 2006. Mechanisms and spread of bacterial resistance to antimicrobial agents. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, D.C., pp. 73–98.

Scottish Environmental Protection Agency. 1998. Sea lice treatment chemicals for cage fish farms: provisional environmental quality standards for azamethiphos. Policy no 17, http://govdocs.aquake.org/cgi/reprint/2003/1025/10250010.pdf.

Scottish Environmental Protection Agency. 1998a SEPA policy on the use of cypermethrin in marine fish farming risk assessment, EQS and recommendations. http://www.sepa.org.uk/aquaculture/policies/index.htm Policy No. 30.

Scottish Environmental Protection Agency. 1999.Emamectin benzoate, an environmental assessment. http://www.sepa.org.uk/policies/index.htm, pp 1–23.

Scottish Environmental Protection Agency. 1999a Calicide (teflubenzuron)—Authorization for use as an infeed sea lice treatment in marine salmon farms.Risk assessment, EQS and recommendations, Policy No 29 http://www.sepa.org.uk/aquaculture/policies/index.htm.

Scottish Environmental Protection Agency, 2006. The occurrence of chemicals used in sea louse treatments in sediments adjacent to marine fish farms: results of screening surveys during 2005. Report. TR060830JBT. iii + 27 pp.

Scottish Environmental Protection Agency 2009 Scottish Pollutant Release Inventory. http://apps.sepa.org.uk/spripa/Search/ByIndustry/Criteria.aspx.Accessed October 13, 2009.

SEARCH, 2006. Sea lice resitance to chemotherapeutants, A handbook in Resistance Management, 2nd Edition. EU funded contract QKK2-CT-00809. accessed August 2009 http://www.rothamsted.bbsrc.ac.uk/pie/search-EU/Handbook.pdf.

Selvik, A., Hansen, P.K., Ervik, A., Samuelsen, O.B., 2002. The stability and persistence of diflubenzuron in marine sediments studied under laboratory conditions and the dispersion to the sediment under a fish farm following medication. Sci. Total Environ. 285 (1–3), 237–245.

Sevatadal, S., Horsberg, T.E., 2003. Determination of reduced sensitivity in sea lice (*Lepeophtheirus salmonis*, Krøyer) against the pyrethroid deltamethrin using bioassays and probit modeling. Aquaculture 2003 (218), 21–31.

Silbergeld, E.K., Graham, J., Price, L.B., 2008. Industrial food animal production, antimicrobial resistance, and human health. Annu. Rev. Public Health 29, 151–169.

Singh, N., Turner, A., 2008. Leaching of copper and zinc from spent antifouling paint particles. Environ. Pollut. 157, 371–376.

Smith, P., 2008. Antimicrobial resistance in aquaculture. Rev. Sci. Tech. Off. Int. Epiz. 27, 243–264.

Smith, P., Hiney, M.P., Samuelsen, O.B., 1994. Bacterial resistance to antimicrobial agents used in fish farming: a critical evaluation of method and meaning. Ann. Rev. Fish Dis. 4, 273–313.

Smith, J.N., Yeats, P.A., Milligan, T.G., 2005. Sediment geochronologies for fish farm contaminants in Lime Kiln Bay, Bay of Fundy. In: Hargrave, B.T. (Ed.), Environmental Effects of Marine Finfish Aquaculture. Springer, Berlin, pp. 221–238.

Sørum, H., 1998. Mobile drug resistance genes among fish bacteria. APMIS 106 (Suppl. 4), 74–76.

Sørum, H., 2000. Farming of Atlantic salmon — an experience from Norway. Acta Vet. Scand. Suppl. 93, 129–134.

Sørum, H., 2006. Antimicrobial drug resistance in fish pathogens. In: Aarestrup, F.M. (Ed.), Antimicrobial Resistance in Bacteria of Animal Origin. ASM Press, Washington, DC, pp. 213–238.

Stauber, J.L., Florence, T.M., 1990. Mechanism of toxicity of zinc to the marine diatom *Nitzschia closterium*. Mar. Biol. 105, 519–524.

Stead, S.M., Laird, L., 2002. Handbook of Salmon Farming. Chichester. Springer. Praxis, U.K.

Stone, J., Sutherland, I.H., Sommerville, C.S., Richards, R.H., Varma, K.J., 1999. The efficacy of emamectin benzoate as an oral treatment of sea lice, *Lepeophtheirus salmonis* (Krøyer), infestations in Atlantic salmon, *Salmo salar* L. J. Fish Dis. 22, 261–270.

Stone, J., Sutherland, I.H., Sommerville, C.S., Richards, R.H., Varma, K.J., 2000a. Field trials to evaluate the efficacy of emamectin benzoate in the control of sea lice, *Lepeophtheirus salmonis* (Krøyer) and *Caligus elongatus* Nordmann, infestations in Atlantic salmon, *Salmo salar* L. Aquaculture 186, 205–219.
Stone, J., Sutherland, I.H., Sommerville, C., Richards, R.H., Varma, K.J., 2000b. Commercial trials using emamectin benzoate to control sea lice (*Lepeophtheirus salmonis*) infestations in Altantic salmon (*Salmo salar* L.). Dis. Aquat. Organ. 41, 141–149.
Sunda, W.G., Tester, P.A., Huntsman, S.A., 1987. Effects of cupric and zinc ion activities on the survival and reproduction of marine copepods. Mar. Biol. 94, 203–210.
Tabche, L.M., Cabrera, I.G., Olivan, L.G., Martinez, M.G., Faz, C.G., 2000. Toxic effects of zinc from trout farm sediments on ATP, protein, and hemoglobin concentrations of antifoulants, antibiotics, parasiticides, anaesthetics and disinfectants *Limnodrilus hoffmeisteri*. J. Toxicol. Environ. Health Part A 59, 575–583.
Teuber, M., 2001. Veterinary use and antibiotic resistance. Curr. Opin. Microbiol. 4, 493–499.
Todar, K., 2008. Antimicrobial agents used in treatm,ent of infectious diseases. Todar's online textbook of bacteriology. http://textbook of bacteriology.net/antimicrobial.html. Accessed Januray 30, 2008.
Treasurer, J.W., Grant, A., 1997. The efficacy of hydrogen peroxide for treatment of farmed Atlantic salmon, *Salmo salar* L. infested with sea lice (Copepoda: Caligidae). Aquaculture 148, 265–275.
Treasurer, J., Wadsworth, S., Grant, A., 2000. Resistance of sea lice *Lepeophtheirus salmonis* (Krøyer) to hydrogen peroxide on farmed Atlantic salmon, *Salmo salar* L. Aquac. Res. 31, 855–860.
Tully, O., McFadden, Y., 2000. Variation in sensitivity of sea lice (*Lepeophtheirus salmonis* (Krøyer)) to dichlorvos on Irish salmon farms in 1991–92. Aquac. Res. 31, 849–854.
Van Dolah, F.M., 2000. Marine algal toxins: origins, health effects and their increased occurrence. Environ. Health Perspect. 108 (Suppl. 1), 133–141.
Waddy, S.L., Burridge, L.E., Hamilton, M.N., Mercer, S.M., Aiken, D.E., Haya, K., 2002. Emamectin benzoate induces molting in American lobster, *Homarus americanus*. Can. J. Fish. Aquat. Sci. 59, 1096–1099.
Waddy, S.L., Merritt, V.A., Hamilton-Gibson, M.N., Aiken, D.E., Burridge, L.E., 2007. Relationship between dose of Emamectin benzoate and molting response of ovigerous American lobsters (*Homarus americanus*). Ecotoxicol. Environ. Saf. 67, 95–99.
Wassenaar, T.M., 2005. Use of antimicrobial agents in veterinary medicine and implications for human health. Crit. Rev. Microbiol. 31, 155–169.
Watzin, M.C., Roscigno, P.R., 1997. The effects of zinc contamination on recruitment and early survival of benthic invertebrates in an estuary. Mar. Pollut. Bull. 34, 443–455.
Webster, N.S., Webb, R., Ridd, M.J., Hill, R.T., Negri, R.P., 2001. The effects of copper on the microbial community of a coral reef sponge. Environ. Microbiol. 3, 19–29.
Weis, J.S., Smith, G., Zhou, T., Bass, C., Weis, P., 2001. Effects of contaminants on behavior: biochemical mechanisms and ecological consequences. BioScience 51, 209–218.
Welch, T.J., Fricke, W.F., McDermott, P.F., White, D.G., Rosso, M.-L., Rasko, D.A., Mammel, M.K., Eppinger, M., Rosovitz, M.J., Wagner, D., Rahalison, L., LeClerc, J.E., Hinahaw, J. M., Lindler, L.E., Cebula, T.A., Carniel, E., Ravel, J., 2007. Multiple antimicrobial resistance in plague: an emerging public health risk. PLoSONE 2 (3), e309.doi.1371/journal.pone.0000309.
Wheatley, S.B., McLoughlin, M.F., Menzies, F.D., Goodall, E.A., 1995. Site management factors influencing mortality rates in Atlantic salmon (*Salmo salar*) during marine production. Aquaculture 136, 195–207.
White, D.G., McDermott, P.F., 2009. Antimicrobial resistance in food borne pathogens. In: Jaykus, L.A., Wang, H.H., Schlesinger, L.S. (Eds.), Food Borne Microbes. Shaping theHost Ecosystem. ASM Press, Washington, DC, pp. 231–265.
Wierup, M., 2001. The Swedish experience of the 1986 year ban of antimicrobial growth promoters, with special reference to animal health, disease prevention, productivity, and usage of antimicrobials. Microb. Drug Resist. 7, 183–190.
Willis, K.J., Ling, N., 2003. Toxicity of emamectin benzoate, an aquaculture pesticide, to planktonic marine copepods. Aquaculture 221, 289–297.
Willis, K.J., Gillibrand, P.A., Cromey, C.J., Black, K.D., 2005. Sea lice treatments on salmon farms have no adverse effects on zooplankton communities: a case study. Mar. Pollut. Bull. 50, 806–816.
Wootten, R., Smith, J.W., Needham, E.A., 1982. Aspects of the biology of parasitic copepods, *Lepeophtheirus salmonis* and *Caligus elongatus* on farmed Atlantic salmon, *Salmo salar*. Proc. R. Soc. Edinb. 81B, 185–197.
Wright, G.D., 2007. The antibiotic resistome: the nexus of chemical and genetic diversity. Nat. Rev. Microbiol. 5, 175–185.
Young, J.S., Gurtisen, J.M., Apts, C.W., Crecelius, E.A., 1979. The relationship between the copper complexing capacity of sea water and copper toxicity in shrimp zoae. Mar. Environ. Res. 2, 265–273.
Zitko, V., 1994. Chemicals in aquaculture (an overview). In: Ervik, A., Kupa Hansen, P., Wennevik, V. (Eds.), Proceedings of the Canada–Norway Workshop on the Environmental Impacts of Aquaculture: Fisken Havet, 13, pp. 97–106.