

Anti-sea lice agents in Norwegian aquaculture; surveillance, treatment trends and possible implications for food safety



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ARTICLE INFO

Keywords:

Aquaculture
Salmon
Surveillance
Veterinary drug
Anti-sea lice agent

ABSTRACT

Sea lice are a major challenge for the Norwegian aquaculture, and to cope with sea lice infections, several physical, biological and chemical treatments are applied. This study presents data on the use of anti-sea lice agents for Norwegian farmed fish from 1992 to 2017, and results from the surveillance of residues of such agents in samples collected from 2002 to 2017. In the period 2002–2007 the use of anti-sea lice agents included emamectin, cypermethrin and deltamethrin. Azamethiphos and flubenzuron were introduced in 2008 and 2009, respectively. In the ongoing surveillance of Norwegian farmed fish, more than 3000 pooled samples have been examined for residues of anti-sea lice agents in the period from 2002 to 2017. Residues were detected in 3% of the samples. Emamectin was detected in 5.0% of the samples analyzed for emamectin, while cypermethrin was detected in 2.1% of the samples analyzed for cypermethrin. Furthermore, residues of diflubenzuron and teflubenzuron were detected in 1.2 and 0.1% of the samples analyzed for these compounds, respectively. None of the other anti-sea lice agents were detected. No measurements were above the respective maximum residue limit (MRL) set by the EU.

1. Introduction

Sea lice (*Lepeophtheirus salmonis*) are ectoparasitic copepods naturally occurring in the sea. Their lifecycle involves eight stages (Hamre et al., 2013). Each stage is separated by a moult (Johnson and Albright, 1991). During the two first naupliar stages and the following infectious copepodid stage, the sea lice are planktonic: they cannot swim directionally against the current but are able to adjust their vertical depth. For the two next stages, the chalimus stages, the lice are attached to the fish. Thereafter follows two pre-adult stages and one adult stage, where the lice are able to move around on the surface of the fish (Hamre et al., 2013). During the last decade, sea lice have become one of the main challenges in the Norwegian fish farming industry. Sea lice feed on the mucus, skin and blood of the hosts, and their impact varies from mild skin damage to stress-induced mortality of individual fish. Lice-infested fish can exhibit reduced appetite, growth rate and food-conversion efficiency (Pike and Wadsworth, 2000). Sea lice also affect wild salmonids, the extent of the impact of aquaculture on sea lice infestation on wild fish is fiercely debated in countries where wild salmonids and farmed salmonids coexist (Krkosek, 2008).

In recent years, several strategies involving physical, biological and chemical approaches have been developed to cope with sea lice in salmon farms. Although the use of cleaner fish, that prey on sea lice (Imsland et al., 2014), and numerous physical treatments (Powell et al., 2015; Stien et al., 2016) has increased, chemical treatment is still an important tool to control the level of infestation. Anti-sea lice agents can be administered by bath treatment or as additives in the feed (Urbina et al., 2019). Since 1992, the chemicals used as bath treatment in Norwegian aquaculture comprise the organophosphates; methidathion, azamethiphos and dichlorvos, the pyrethroids; pyrethrins, cypermethrin and deltamethrin, and hydrogen peroxide. The avermectin; emamectin, and the flubenzuron; teflubenzuron and diflubenzuron have been used as additives in the feed.

The anti-sea lice agents differ in their mode of action and efficacy. The organophosphates are acetylcholinesterase inhibitors, they are effective against adult and pre-adult stages of sea lice (Roth et al., 1996). The pyrethroids disrupt the sodium channel function, and are effective in both chalimus, preadult and adult stages of sea lice (Burka et al., 1997). Hydrogen peroxide is a strong oxidizing agent and cause sea lice to separate from its host (Thomassen, 1993), and is most effective

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<https://doi.org/10.1016/j.aquaculture.2020.735044>

Received 19 September 2019; Received in revised form 28 January 2020; Accepted 29 January 2020

Available online 30 January 2020

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against lice in their mobile life stages (Treasurer and Grant, 1997). Emamectin blocks nerve transmission, causing paralysis and death of the sea lice (Arena et al., 1995; Vassilatis et al., 1997). Emamectin has a high efficacy against all parasitic stages of sea lice on farmed salmon, and treatment also prevents recruitment of new lice for approximately 10 weeks (Stone et al., 2000). Flubenzurons inhibit chitin synthesis, and their efficiency are therefore restricted to the moulting stages of sea lice, and no effect is thus perceived on adult lice that has already formed their final exoskeleton (Branson et al., 2000; Burka et al., 1997).

Norway is one of the main producers and exporters of marine farmed fish (FAO, 2016). In 2017, approximately 1.3 mill tons of farmed fish, mainly Atlantic salmon (*Salmo salar*) were produced. The scope of the present study is to delineate the use of anti-sea lice agents, and assess their possible impact on food safety. Prior to market authorization in Norway any veterinary drug requires approval by the European Commission (EU 37/2010) and The Norwegian Medicines Agency (NoMA). Drugs intended for therapeutic use in farmed fish require prescriptions from veterinarians or fish health biologists. From 1989, it has been mandatory for both prescribing veterinarians and feed mills to send a copy of each prescription, first to the Norwegian Government Fish Inspection and Quality Control Service (NFCS) and thereafter from 2004 to the Norwegian Food Safety Authority (NFSA). Further, to ensure food safety, a systematic surveillance system is obliged under the current EU regulations (European Commission, 1996).

The aim of this study is to describe the amount of anti-sea lice agents used in Norwegian aquaculture and using data on residues from the Norwegian monitoring program on farmed fish, to describe the possible implications in regards to food safety.

2. Materials and methods

2.1. The use of veterinary drugs in Norway

Statistics on drugs sold for use in Norwegian farmed fish were obtained from the Norwegian Institute of Public Health (NIPH). To calculate the annually treated biomass, the amount of active substance was adjusted using the dosage described in the package leaflets (Table 1). The treatment ratio was calculated from the relation between the annually treated biomass and the biomass slaughtered (Directorate of Fisheries, 2019).

Table 1
Biomass fish treated per kilo drug.

Chemical	Dosage bath treatment	Dosage feed	Biomass fish treated per kilo drug
	(g/m ³)	(mg/kg fish per day)	
Metrifonate	50		1000
Dichlorvos	1		50,000
Pyrethrins	0.1		500,000
Azamethiphos	0.1		500,000
H ₂ O ₂	1500		33
Diflubenzuron*		3	23,810
Teflubenzuron**		10	14,285
Cypermethrin (until 1998)	0.005		10,000,000
Cypermethrin (after 1998)	0.015		3,333,333
Deltamethrin	0.003		16,666,667
Emamectin**		0.05	2,857,143

*daily for 14 days
**daily for 7 days

The dosage used in the calculations are specifies for each anti-sea lice drug. For bath treatments it is estimated that each m3 contains 50 kg salmonids.

2.2. Sampling and sample preparation

Data was obtained from the ongoing surveillance of Norwegian farmed fish according to council directive 96/23/EC, on measures to monitor certain substances and residues thereof in live animals and animal products (European Commission, 1996). The total number of samples collected in the surveillance is dependent on the production volume (European Commission, 1996). From 2002 to 2017 the production of Norwegian farmed salmonids increased from 546,000 t to 1,285,000 t, leading to an increase in the total number of samples to be monitored. The number of samples examined for each veterinary drug is set by the Norwegian Food Safety Authority (NFSA). The priorities are mainly based on the prescription of pharmaceuticals used in the industry. The samples were collected annually from 2002 to 2017, throughout the season in all fish-producing regions in Norway. The samples were collected at processing plants by inspectors from the Directorate of Fisheries until 2004, and by inspectors from the NFSA from 2005. The samples include salmonid species in Norwegian aquaculture, primarily Atlantic salmon (*Salmo salar*) (n = 2993), and to a lesser extent rainbow trout (*Oncorhynchus mykiss*) (n = 219) and Arctic char (*Salvelinus alpinus*) (n = 2). Standardised muscle samples, the Norwegian Quality Cut (NQC) (Johnsen et al., 2011), were collected from five fish from the same net pen, and frozen (-20 °C) in sealed plastic bags before sent in a frozen state to The Institute of Marine Research (IMR). Upon arrival at IMR, composite samples were prepared by pooling equal amounts of muscle from five individual fish. The samples were stored at -20 °C prior to analysis. For all samples, a back-up sample was stored. From 2014, the skin was included in the back-up sample. The MRL for fish is set for muscle and skin in natural proportions (European Commission, 2010), where the proportions between muscle and skin is 9:1. Therefore, any detection of anti-sea lice agents in the muscle sample led to reanalysis of the back-up sample where skin was included. For these samples the reported results are from muscle and skin.

2.3. Analyses

The samples were analyzed for the anti-sea lice agents emamectin, diflubenzuron, teflubenzuron, cypermethrin, deltamethrin, azamethiphos or/and dichlorvos. From 2002, both sample preparation and instrumentation have improved, and the methods used have been amended. Hence, the limit of quantification has been modified for several of the methods (Supplement table 2). In addition, there has been a development from single analyte methods, towards including several analytes in the same method, giving more results for each sample. A blank sample and control sample have been included together with standards for all methods.

2.3.1. Analysis of emamectin

From 2004 to 2014, samples analyzed for emamectin were prepared as described in Skilbrei et al. (2008) and determined by LC-MS (Hamre et al., 2011). From 2015, emamectin was analyzed by two methods. Most of the samples were analyzed by using emamectin-d3 as internal standard, before acetonitrile was used for extraction. The extract was evaporated and resolved in a mix of methanol and water. Emamectin was determined by LC-MS/MS using electrospray ionization (ESI) in a positive MRM mode. For a part of the samples, a mix of acetonitrile and water were used for extraction. Petroleum ether was used to remove fat, and the samples were analyzed by LC-MS/MS using electrospray ionization (ESI) in a positive MRM mode.

2.3.2. Analyses of teflubenzuron and diflubenzuron

From 2002 to 2014, diflubenzuron was analyzed by LC-MS (Hamre et al., 2013). Teflubenzuron was determined by a similar method as diflubenzuron as described earlier (Samuelsen et al., 2014). From 2015, diflubenzuron and teflubenzuron were analyzed by two methods. Most

of the samples were analyzed by a method using diflubenzuron-d4 as internal standard for both diflubenzuron and teflubenzuron. The flubenzurons were extracted by acetone, and the extract were purified by solid phase extraction (SPE) before analysis by LC-MS/MS using ESI in a negative MRM mode (Olsvik et al., 2015). For a part of the samples, a mix of acetonitrile and water were used for extraction. Petroleum ether was used to remove fat, and the samples were analyzed by LC-MS/MS using electrospray ionization (ESI) in a positive MRM mode.

2.3.3. Analyses of cypermethrin and deltamethrin

From 2002 to 2014, cypermethrin and deltamethrin were extracted by acetone. A liquid-liquid extraction was performed to purify the extract. Additional sample clean-up was performed by gel permeation chromatography (GPC) followed by solid phase extraction (SPE). The sample was analyzed by GC-MS with electron impact (EI) ionization. From 2015, the pyrethrins were soxhlet extracted using methyl-tert-butyl ether. Thereafter sample clean-up was performed by gel permeation chromatography (GPC) followed by a clean-up process using primary secondary amine. The sample was analyzed by GC-MS/MS.

2.3.4. Analyses of azamethiphos and dichlorvos

From 2004 to 2006, azamethiphos was extracted by ethyl acetate. A liquid-liquid extraction was used to purify the extract. Additional sample clean-up was performed by SPE. The sample was analyzed by HPLC-FLD. In the same period, dichlorvos was extracted by a mix of acetone and cyclohexane. Sample clean-up was performed by SPE. The sample was analyzed by GC-MS with EI ionization. From 2010 to 2014, azamethiphos and dichlorvos were extracted by acetone. The extract was purified by GPC and analyzed by GC-FLD. From 2015, azamethiphos and dichlorvos were extracted by a mix of acetonitrile and water, petroleum ether was used for samples clean-up, and the samples were analyzed by LC-MS/MS using electrospray ionization (ESI) in a positive MRM mode.

3. Results

3.1. Use of anti-sea lice agents in Norwegian farmed fish

Anti-sea lice agents used in Norway in the period 1992 to 2017 include metrifonate, pyrethrins, dichlorvos, azamethiphos, cypermethrin, deltamethrin, emamectin, teflubenzuron, diflubenzuron and hydrogen peroxide (Table 2). In 1992, only metrifonate and dichlorvos were used against sea lice, however, the following years several other compounds were included in the treatments. From 2002 to 2007 the drugs used comprised of cypermethrin, deltamethrin and emamectin. In 2008, azamethiphos was also used. From 2009 and onwards, treatments also included use of hydrogen peroxide, teflubenzuron and diflubenzuron. Until 1998, the total amount of anti-sea lice agents used (in kilograms) were high, ranging between 2000 and 700,000 kg (Table 2). Between the years 1999 to 2008, the use of anti-sea lice agents was lower, ranging from 98 to 329 kg active compound. From 2008 to 2009 the amount used increased from 218 kg to 314,000 kg active compound and continued to increase to 43 million kg active compound in 2015. Thereafter, the amount decreased to 9 million kg in 2017.

The estimated biomass fish (tonnes) treated with anti-sea lice agents in the period from 1992 to 2017 is shown in Fig. 1a. From 1992 to 2008, the treatment rate; biomass salmonids (tonnes) treated per biomass salmonids (tonnes) produced, was rather stable, varying from 0.6 to 1.5 times per year (Fig. 1b). Since 2008, the biomass produced of farmed salmon, rainbow trout and arctic char were lower than the biomasses treated, implicating that the annual treatment ratio is above one (Grave et al., 2004). In 2014, the ratio between produced and treated biomass peaked with an annual treatment ratio of 5.7. From 2015, the treated biomass declined reaching an annual treatment ratio

below 1.0 in 2017.

3.2. Residues of veterinary drugs

From 2002 to 2017, more than 3000 pooled samples were examined for residues of anti-sea lice agents (Supplement table 1). The analyses include dichlorvos, azamethiphos, diflubenzuron, teflubenzuron, cypermethrin, deltamethrin or/and emamectin. During this period, residues of emamectin, cypermethrin, diflubenzuron and teflubenzuron were detected, but no residues were detected at concentrations above the EU maximum residue limit (European Commission, 2010) (Fig. 2). However, the two highest measured levels of emamectin corresponded to 94% and 34% of the MRL. The highest level detected of cypermethrin was 30% of the MRL, whereas the highest concentration of diflubenzuron and teflubenzuron were 1% and 3% of the MRL, respectively.

4. Discussion

Sea lice represent a major challenge for marine aquaculture. Here, we assess the use of anti-sea lice drugs from 1992 to 2017 and the presence of medical residues in farmed salmonids from 2002 to 2017. Although a severe increase in the use of anti-sea lice agents during the last two decades was observed, we did not detect residue levels above the MRL in the fillet of the farmed fish.

4.1. Use of anti-sea lice agents in Norwegian farmed fish

While the amount of anti-sea lice agents used decreased in the end of the 90s and remained low until 2009, the biomass treated were relatively stable from 1992 to 2008. The reason for this discrepancy is the shift from therapeutics with low potency, like metrifonate, dichlorvos and hydrogen peroxide towards more potent compounds like cypermethrin, deltamethrin and emamectin. Hence, the amount of active compound used, but not the amount biomass treated is reduced in this period. From 2008 to 2009, we observed a steep increase in the use of anti-sea lice agents. However, the dosage of the different anti-sea lice agents varies greatly and in 2009 treatment also included hydrogen peroxide. Whereas 1 kg deltamethrin is used to treat 17 million kg fish, 1 kg hydrogen peroxide is used to treat only 33 kg fish. In order to adjust for the differences in dosage for the various anti sea lice agents the biomass fish treated were calculated using the prescription data. Hence, use that are not in accordance with the prescription data will therefore not be identified. Due to problems with resistance, off-label use including increasing dosage level and use of combination treatments of two or more therapeutics have been conducted (Jackson et al., 2018). Such use will lead to an overestimation of the biomass treated.

The observed increase in both the amount of therapeutics used, and biomass treated from 2009 and onwards, is most likely due to reduced sensitivity or resistance to the therapeutics used. Reduced sensitivity or resistance towards azamethiphos, the pyrethroids, emamectin and hydrogen peroxide is documented, but so far, no cases with confirmed insensitivity towards teflubenzuron or diflubenzuron are reported (Aaen et al., 2015). One major cause of the rapid spread of resistance towards azamethiphos, the pyrethroids, emamectin and hydrogen peroxide may relate to the lack of available alternative treatments when resistance emerged in 2008–2009. Hence, the fish health services used the same compounds in combination or at escalating doses to attain the required regulatory limit of 0.5 adult female lice per fish. When resistance towards a drug is emerging, any application of the drug will rapidly exaggerate the resistance situation. As this was a widespread practice after 2008, the problems escalated, resulting in an increase in doses and frequency of treatments, a dramatic increase in total use of the different compounds is observed. An official annually monitoring of resistance to anti-sea lice agents in salmon lice has been conducted since 2013 (Helgesen et al., 2018). The observed decreased treatment

Table 2
Chemicals used against sea lice from 1992 to 2017.

Year	Cypermethrin	Deltamethrin	Emamectin	Pyrethrins	Metrifonate	Dichlorvos	Azamethiphos	Diflubenzuron	Teflubenzuron	Hydrogen peroxide
1992	-	-	-	-	1,946	3,115	-	-	-	-
1993	-	-	-	-	1,779	2,470	-	-	-	7,10,000
1994	-	-	-	32	1,227	1,147	389	-	-	2,90,000
1995	-	-	-	26	-	395	738	-	-	3,40,000
1996	23	-	-	9	-	161	606	160	610	1,60,000
1997	28	-	-	18	-	36	315	361	1,510	20,000
1998	3	19	-	-	-	-	182	437	1,334	-
1999	19	11	4	-	-	-	14	50	231	-
2000	73	23	30	-	-	-	-	12	62	-
2001	69	19	12	-	-	-	-	-	28	-
2002	62	23	20	-	-	-	-	-	-	-
2003	59	16	23	-	-	-	-	-	-	-
2004	55	17	32	-	-	-	-	-	-	-
2005	45	16	39	-	-	-	-	-	-	-
2006	49	23	60	-	-	-	-	-	-	-
2007	30	29	73	-	-	-	-	-	-	-
2008	32	39	81	-	-	-	66	-	-	-
2009	88	62	41	-	-	-	1,884	1,413	2,028	3,08,000
2010	107	61	22	-	-	-	3,346	1,839	1,080	30,71,000
2011	48	54	105	-	-	-	2,437	704	26	31,44,000
2012	232	121	36	-	-	-	4,059	1,611	751	25,38,000
2013	211	136	51	-	-	-	3,037	3,264	1,704	82,62,000
2014	162	158	172	-	-	-	4,630	5,016	2,674	3,15,77,000
2015	85	115	259	-	-	-	3,904	5,896	2,509	4,32,46,000
2016	48	43	232	-	-	-	1,269	4,824	4,209	2,65,97,000
2017	8	14	128	-	-	-	204	1,803	293	92,77,000

Chemicals used against sea lice from 1992 to 2017 (kg active substance).

Data are presented by numbers and data bars. For each compound the databars are normalized to maximum use. Colors visualize different ranges of use, based on the maximum use. Green: > 0–500; Yellow; > 0–10,000; red: > 0–50,000,000.

Source: Norwegian Institute of Public Health.

ratio between 2014 and 2017, relate to the increased use of non-chemical approaches (Overton et al., 2018; Helgesen et al., 2018). In 2014, various forms of mechanical treatment were performed 176 times. The use of mechanical treatments increased the following years and reached 1665 in 2017 (Barentswatch, 2018). In addition, cleaner fish added to the net pens has been used to reduce the number of sea lice in the farms. The number of cleaner fish increased from 26 million in 2014 to 51 million in 2017 (Directorate of Fisheries, 2017).

Sea lice is also a major problem in other salmonid producing countries. In Chile, the second largest producer of salmonids, data from 2007 to 2012 showed that the biomass of salmonids treated had been higher than the slaughter volume for the hole period, in 2012 the biomass of salmonids treated was more than nine times the slaughter volume (Helgesen et al., 2014). In Scotland, treatment rate, calculated as the number of treated sites divided by the number of occupied sites, increased from approximately 1.88 treatments per year in 2005 to 3.39 treatments per year in 2011 (Murray, 2016). Data from the USA showed that in Washington, with an annual production of around 5000 t, no anti sea lice agents were used from 2012 to 2017. However, in Maine, with an annual production of around 15,000 t, emamectin was used in 13 of 21 production cycles from 2014 to 2017, also hydrogen peroxide was used for treatment, but no further anti sea lice agents were used (Love et al., 2020).

4.2. Residues of veterinary drugs

Until 2006, no residues of anti-sea lice agents were detected in the samples analyzed (Fig. 2). From 2006 and onwards residues of emamectin have been found in samples each year. Residues of cypermethrin was detected for the first time in 2010, since then it has been found most years. Residues of diflubenzuron were detected in 2015 to 2017, while residues of teflubenzuron was found in one sample in 2016. The highest numbers of positive samples were detected in 2015 and 2016. In 2015, residues of anti-sea lice agents were detected in 21 samples, co-occurring with the highest registered use of anti-sea lice agents (in kilograms). In 2016, the use (in kilograms) declined, and a steep decrease was registered in 2017, but a co-occurring decrease in number of positive samples was not observed. Of note, however, emamectin represented a high fraction of the positive samples in 2016 and 2017, and the reduction in use of emamectin was not as pronounced as the reduction in total use. For diflubenzuron, the LOQ was lowered from 10 µg/kg to 1.0 µg/kg in 2015 (Supplement table 2). Since eight of the ten detections of diflubenzuron were within the interval of 1.0 to 10 µg/kg, introduction of this new LOQ could explain the increased detection of diflubenzuron after 2015 (Supplement table 3). Moreover, results from cypermethrin monitoring suggests a steady detection rate throughout the years of analyses. However, the lowering of the LOQ for cypermethrin from 10 µg/kg to 5.0 µg/kg in 2015 suggest a higher detection rate of this compound before 2015 could be masked, since six

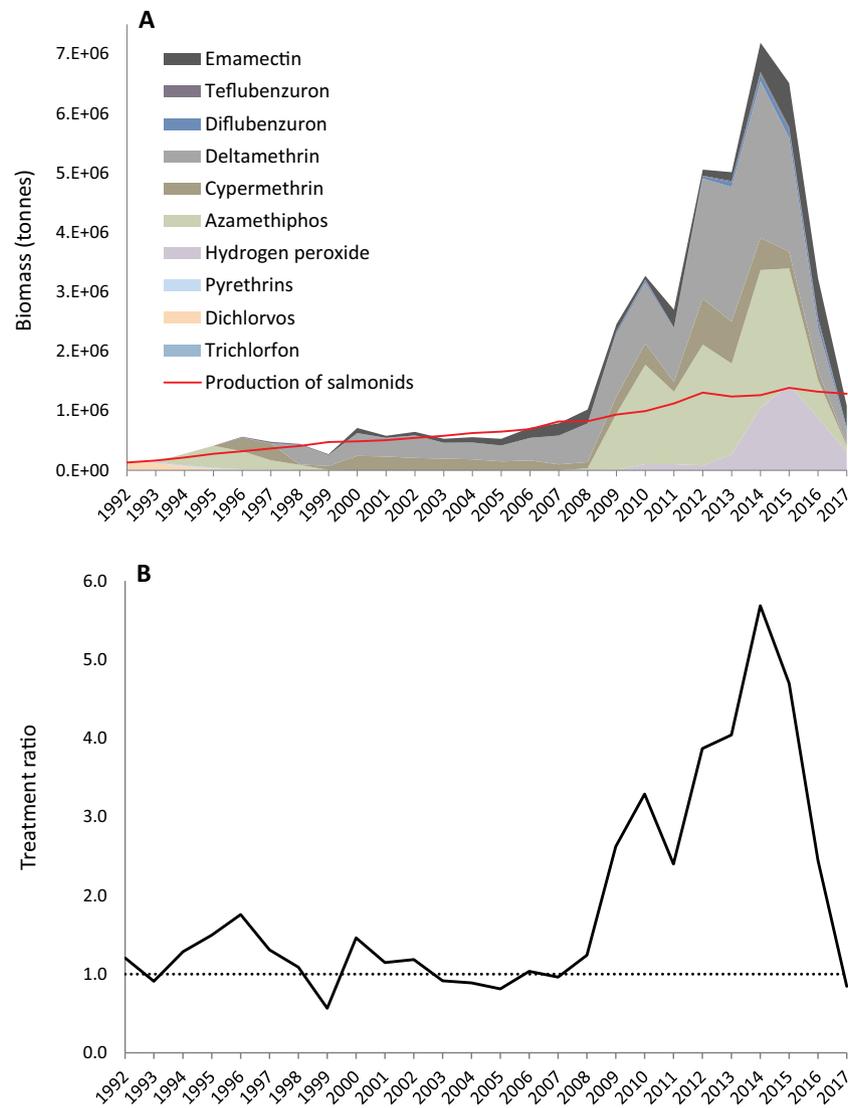


Fig. 1. The biomass of salmonids treated with different anti-sea lice agents from 1992 to 2017. A. Biomass of salmonids treated with anti-sea lice agents. B. Treatment ratio of anti-sea lice agents. Black line represents biomass treated (tonnes) per biomass produced (tonnes). Dotted line represents a treatment ratio of one; the amount salmonids treated is equal to the amount salmonids produced.

out of nine samples, post 2015, were within the interval of 5 to 10 $\mu\text{g}/\text{kg}$ (Supplement table 3).

Data on residues of anti-sea lice agents in fish is scarce. However, monitoring data from the EU (European Commission, 1996) shows that in 2016, residues of emamectin above the MRL were detected in three of 562 targeted samples analyzed (EFSA, 2018). While no residues of anti-sea lice agents above the MRL were detected in 2017 (EFSA, 2019). Data on results of residues above the LOQ but below the MRL were not available. Violation data from EU, United States, Canada and Japan from 2002 to 2009 shows that 3% of the drug violations in finfish in Canada were caused by avermectins (Love et al., 2011). However, most of the violations in both the EU, United States, Canada and Japan were caused by compounds that are not authorized to use in the EU and residues of antibiotics.

4.3. Food safety

Residues of emamectin, cypermethrin, diflubenzuron and teflubenzuron have been detected in the samples of fish, however, none of the samples had residue levels above the MRL set by the EU. The most commonly found anti-sea lice agent was emamectin. The highest level

measured was 94 $\mu\text{g}/\text{kg}$, and hence, emamectin was the anti-sea lice agent that had residues closest to the MRL. In order to ensure consumer safety, EU has determined an acceptable daily intake (ADI) value of 0.5 $\mu\text{g}/\text{kg}$ body weight per day for emamectin (European Food Safety Authority, 2012). For a person, with a body weight of 60 kg, consumption of 200 g of salmon, with the maximum measured emamectin level of 94 $\mu\text{g}/\text{g}$, would contribute to 63% of the ADI. During medication, anti-sea lice agents can be distributed around the farms, and residues may be found in the wild fauna (Wang et al., 2019; Samuelsen et al., 2015). In addition, emamectin is also approved as a pesticide. Therefore, it cannot be excluded that intake of farmed fish, with emamectin level close to the MRL, together with other food sources containing emamectin residues could lead to an exposure that will exceed the ADI. However, the ADI is based on chronic exposure, therefore, it will be more appropriate to compare the intake with the acute reference dose (ARfD). The European Food Safety Authority (EFSA) has established an ARfD for emamectin of 10 $\mu\text{g}/\text{kg}$ bw (European Food Safety Authority, 2012). An intake of 200 g salmon, with emamectin level close to the MRL, will only contribute to 3% of the ARfD.

Since all samples represent fish ready for human consumption, fish that received any veterinary drugs have had a withdrawal period before

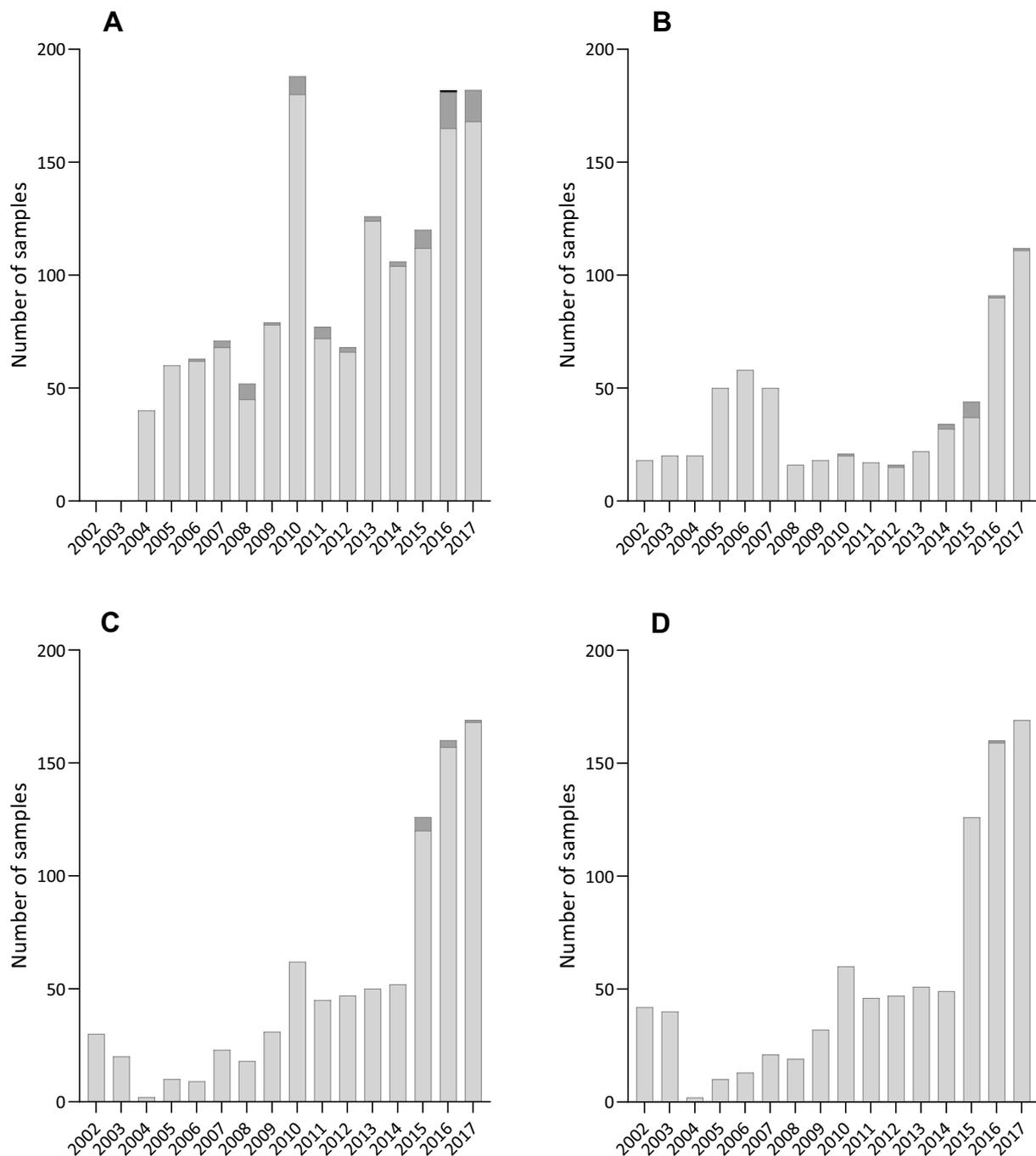


Fig. 2. The number of samples, and the level of residues of anti-sea lice agents detected in salmonids from 2002 to 2017. Colors visualizes percentage of MRL. Light grey: < LOQ, grey: > LOQ – 50% of MRL, black: > 50% of MRL. A. Emamectin. B. Cypermethrin. C. Diflubenzuron. D. Teflubenzuron.

slaughtering. The withdrawal period is established to ensure that the food do not contain residues of veterinary drugs in excess of the established MRL. The absence of data above the corresponding MRL values indicates that the established withdrawal periods are appropriate.

The MRL set by the EU is established based on the knowledge available at the time being. New data can lead to a review of the MRL. For diflubenzuron, concern has been raised regarding p-chloroaniline, a possible impurity and metabolite of diflubenzuron. After a re-evaluation (Committee for Medicinal Products for Veterinary Use, 2018), the MRL for diflubenzuron will be reduced from 1000 µg/g to 10 µg/g (European Commission, 2019). From 2002 to 2017, residues of diflubenzuron above 10 µg/g were detected in two pooled samples. An increase in withdrawal time should be considered to avoid residue

levels above the MRL.

5. Conclusion

This study presents the use of anti-sea lice agents in Norwegian aquaculture from 1992 to 2017, and the presence of residues of these agents in farmed fish from 2002 to 2017. The amount of anti-sea lice agents used increased from 1992 to 2015 but decreased in 2016 and 2017. All samples studied demonstrated compliance to EU regulations. Based on the established MRLs, the use of veterinary drugs against sea lice does not seem to affect the food safety of Norwegian farmed fish.

Funding

The Norwegian Food Safety Authority funded the analyses and was responsible for the collection of samples.

Declaration of Competing Interest

None.

Acknowledgement

The authors would like to thank personnel at the Sample reception unit and the Chemistry and contaminant lab, at The Institute of Marine Research, for sample preparation and analyses.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.aquaculture.2020.735044>.

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