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Opinion of the Scientific Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety

Adopted 5th of September 2007

Risk assessment of the use of XyRex® formulations on fish used for production of fish meal to fish and animal feed. Effects on animal health, human health and the environment

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Summary

The XyRex® formulations are antimicrobial agents with sodium chlorite as the active substance. The Norwegian Food Safety Authority has received a request to authorise XyRex® formulations for use in refrigerated sea-water (RSW) tanks on board fishing vessels for pelagic fish caught for production of fish meal/fish oil for use in animal feed. The use of XyRex® formulations on fish for human consumption is not approved in Norway.

It is a premise that use of food processing aids should not pose a threat to health of humans or animals. The XyRex®-containing RSW will not be completely drained off before the production of fish meal/fish oil. The Norwegian Food Safety Authority has therefore requested The Norwegian Scientific Committee for Food Safety (VKM), Panel on Animal Feed, to assess the safety to humans and animals with regard to the use of XyRex® formulations with 12.5 ppm sodium chlorite, as recommended by the producer, in RSW on board fishing vessels for pelagic fish. The Norwegian Scientific Committee for Food Safety appointed an *ad hoc* group to answer the request from the Norwegian Food Safety Authority. The report from the *ad hoc* group has been discussed and approved by VKM's Scientific Panel on Animal Feed.

The use of the XyRex® formulations will mainly result in the release of sodium chlorite and sodium chlorate, which therefore are the components in the XyRex® formulations that may cause concerns for health risks. The amounts of these substances formed and transferred with the fish to the fish meal, fish meal-containing feed, and ultimately to the fish, meats, milk and eggs from animals eating the fish meal, are not known. Therefore, this evaluation is based on a worst-case scenario of transfer of the maximum amounts of these residues from the XyRex®-formulations, and the available information on theoretical transfer in each step from the RSW tanks on board fishing vessels into fish and animal feed and human foods.

The estimated exposures of farmed fish and domestic animals to sodium chlorite and sodium chlorate in their fish meal-containing feed are all below the tolerable daily intake (TDI) value of 30 µg/kg body weight (bw)/day, set for both sodium chlorite and sodium chlorate. Therefore, no adverse effects on fish or animal health would be expected by exposure to sodium chlorite and sodium chlorate from the use of XyRex® formulations in RSW on board the fishing vessels catching fish being used for fish meal being included in fish and animal feed.

The intakes of sodium chlorite and sodium chlorate for humans from consumption of farmed fish or domestic animals being fed on fish meal from XyRex®-treated fish were estimated assuming the worst-case scenario that all the sodium chlorite and sodium chlorate the fish and animals were exposed to were accumulating in their meats, or transferred to milk and eggs. These estimated average and high exposures to farmed salmon, pork, beef, chicken, turkey, milk and eggs are well below the TDI values for both sodium chlorite and sodium chlorate of 30 µg/kg bw/day. In reality, a significant amount of the sodium chlorite in the XyRex® formulations will be depleted during the disinfection process and not end up in the fish meal and thereafter in the feed, and both sodium chlorite and sodium chlorate will to a large extent be excreted rather than accumulated in the meats of fish and animals, or in milk and eggs. Therefore, the real exposure values are likely to be lower than the values estimated here.

The likelihood of by-product formation from the specified use of XyRex® formulations has also been addressed. Because the temperatures used for cooking and drying during fish meal

production are well below the temperatures where dioxins and furans are formed, the formation of these substances during production is unlikely. Also, since the amounts of chlorine compounds present with the fish are low, we regard any significant health risks from chlorination by-products to be unlikely. However, further data might be needed to confirm that chlorinated compounds are not generated to a significant extent from the use of XyRex® formulations. Based on the available data on reactions of acidified sodium chlorite (ASC) and chlorine dioxide with proteins and lipids in poultry carcasses or fish, a significant formation of harmful, i.e. mutagenic, by-products from the use of the XyRex® formulations on fish is not expected. A negative effect on the quality of the fish oil, if substantial oxidation is taking place, can not be ruled out.

Release of RSW in harbour areas is forbidden by law in Norway. The concentrations of sodium chloride and sodium chlorate in RSW being released from the fishing vessels to open sea during transport will rapidly be diluted around the release point, and are therefore not likely to have any adverse effects. The specified use of XyRex® formulations in RSW tanks on board fishing vessels is therefore not expected to be of significant environmental concern.

The Panel on Animal feed has not evaluated the disinfecting activity claimed for the XyRex® products, nor any potential for development of bacterial resistance after use of the XyRex® products, since these questions were not asked by the Norwegian Food Safety Authority.

Sammendrag (Norwegian summary)

XyRex®-produkter er antimikrobielle agens med natriumkloritt som aktivt stoff. Mattilsynet har mottatt en henvendelse om godkjenning av XyRex®-produkter for bruk i tanker med nedkjølt sjøvann (RSW) ombord på fiskebåter for pelagisk fisk som skal gå til produksjon av fiskemel/fiskeolje til bruk i dyrefôr. Bruk av XyRex®-produkter på fisk som skal gå til humant konsum er ikke godkjent i Norge.

Det er en forutsetning at bruk av prosesshjelpemidler ikke skal utgjøre en helserisiko for mennesker eller dyr. XyRex®-inneholdende RSW vil ikke bli fullstendig avrent fra fisken før denne går til produksjon av fiskemel/fiskeolje. Mattilsynet har derfor bedt Vitenskapskomiteen for mattrygghet (VKM), Faggruppe for fôr til terrestriske og akvatiske dyr, om å vurdere helsemessig risiko for mennesker og dyr hvis XyRex®-produktene med 12,5 ppm natriumkloritt, som anbefalt av produsenten, blir brukt i RSW-tanker ombord på fiskebåter for pelagisk fisk. Faggruppen nedsatte en *ad hoc*-gruppe som har svart på spørsmålene fra Mattilsynet. Rapporten fra *ad hoc*-gruppen er diskutert og godkjent av Faggruppen for fôr til terrestriske og akvatiske dyr.

Bruken av XyRex®-produktene vil hovedsaklig resultere i frigjøring av natriumkloritt og natriumklorat, som derfor er de komponentene i XyRex®-produktene som kan gi bekymring når det gjelder en eventuell helserisiko. Mengdene av disse stoffene som dannes og overføres med fisken til fiskemel, fiskemel-inneholdende fôr, og til sist i fisk, kjøtt, melk og egg fra dyr som spiser fiskemel i fôret, er ikke oppgitt. Denne vurderingen er derfor basert på en verste-fallsberegning med overføring av maksimum mengder av disse stoffene fra XyRex®-produktene, og den tilgjengelige informasjonen om teoretisk overføring i hvert trinn fra RSW-tankene ombord på fiskebåter til fisk og dyre-fôr og menneske-mat.

De estimerte eksponeringene av oppdrettsfisk (hovedsaklig laks) og husdyr for natriumkloritt og natriumklorat i deres fiskemel-inneholdende fôr er alle under verdien for det tolerable daglige inntaket (TDI) på 30 µg/kg kroppsvekt/dag satt for både natriumkloritt og natriumklorat. Derfor forventes ingen skadelige effekter på fiske- eller dyrehelse etter eksponering for natriumkloritt og natriumklorat fra bruk av XyRex® i RSW ombord på fiskebåter for pelagisk fisk som skal gå til produksjon av fiskemel/fiskeolje til bruk i fiske- og dyrefôr.

Inntakene av natriumkloritt og natriumklorat hos mennesker fra konsum av oppdrettsfisk eller kjøtt, eller melk og egg, fra husdyr som hadde blitt fôret med fiskemel fra XyRex®-behandlet fisk ble estimert ut fra en verstefalls-beregning hvor man antok at all natriumkloritt og natriumklorat som fisken og husdyrene ble eksponert for akkumulerte i fisken og kjøttet, eller ble overført til melk og egg. Disse estimerte verdiene for gjennomsnittlig og høyt inntak av oppdrettslaks, svinekjøtt, storfekjøtt, kylling, kalkun, melk og egg var langt under TDI-verdiene for både natriumkloritt og natriumklorat på 30 µg/kg kroppsvekt/dag. I virkeligheten vil en betydelig mengde av natriumkloritten bli brukt opp under desinfeksjonsprosessen og ikke ende opp i fiskemelet og deretter i fôret, og både natriumkloritt og natriumklorat vil i stor grad bli utskilt heller enn akkumulert i fisken og kjøttet fra husdyra, eller i melk og egg. Derfor er de reelle eksponeringsverdiene sannsynligvis lavere enn de verdiene som er estimerte her.

Dannelse av biprodukter fra den spesifiserte bruken av XyRex®-produktene har også blitt vurdert. Fordi temperaturene som brukes for koking og tørking under produksjon av fiskemel er langt under de temperaturene hvor dioksiner og furaner dannes, er dannelse av disse stoffene i denne sammenhengen usannsynlig. Også fordi mengdene av klor-forbindelser til stede med fisken er lave, anser vi at helserisiko fra klorerte biprodukter er lite sannsynlig. Men mer data kan være nødvendig for å bekrefte at klorholdige biprodukter ikke dannes i signifikant grad fra bruken av XyRex®-produktene. Ut fra data om reaksjoner av surgjort natriumkloritt (ASC) og klordioksyd med proteiner og lipider i kyllingslakt eller fisk, forventes ikke en signifikant dannelse av skadelige, dvs. mutagene, biprodukter etter bruk av XyRex®-produktene. En negativ effekt på kvaliteten av fiskeoljen hvis oksidering av fettsyrer skjer i betydelig grad, kan imidlertid ikke utelukkes.

Utslipp av vann fra RSW-tanker i havneområder er forbudt ved lov i Norge. Konsentrasjonene av natriumkloritt og natriumklorat i vannet som slippes ut fra RSW-tankene fra fiskebåter i åpen sjø under transport vil raskt bli fortynnet vekk fra utslippspunktet, og vil derfor sannsynligvis ikke ha noen skadelige effekter. Den spesifiserte bruken av XyRex®-produkter i RSW-tanker ombord på fiskebåter forventes derfor ikke å gi noen grunn til bekymring for miljøet.

Faggruppen for fôr til terrestriske og akvatiske dyr i VKM har ikke vurdert den desinfiserende virkningen som XyRex®-produktene er påberopt å ha, og heller ikke eventuelt potensiale for utvikling av bakterieresistens etter bruk av XyRex®-produktene, siden disse problemstillingene ikke ble reist i bestillingen fra Mattilsynet.

Glossary

ASC	acidified sodium chlorite
bw	body weight
EFSA	the European Food Safety Authority
E(L)C_{50}	effective (lethal) concentration 50%: the concentration that causes effects (death) in 50% of the tested organisms
EPA	the United States Environmental Protection Agency
IARC	the International Agency for Research on Cancer
IPCS	the International Programme on Chemical Safety
LD_{50}	lethal dose 50%: the dose that causes death in 50% of the tested animals
LOAEL	lowest observed adverse effect level: the lowest dose of a substance for which an adverse effect can be observed in a long-term toxicity animal study
LOEC	lowest observed effect concentration: the lowest observed concentration that causes effect on the tested population
NOAEL	no observed adverse effect level: the highest dose of a substance for which no adverse effects can be observed in a long-term toxicity animal study
NOEC	no observed effect concentration: the highest concentration of a substance that does not give any observable effects on the tested population
NTP	the National Toxicology Program, U.S.A.
PCDD	polychlorodibenzo-*p*-dioxins
PCDF	polychlorodibenzo-furans
RfD	reference dose: used in U.S.A. as an estimate of a daily oral exposure to humans that is likely to be without an appreciable risk of deleterious effects during a lifetime (similar to TDI)
RSW	refrigerated sea-water
TDI	tolerable daily intake: an estimate of the amount of a contaminant in food or drinking water, expressed on a body mass basis, usually mg/kg body weight, which can be ingested daily over a lifetime by humans without appreciable health risks
VKM	The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet)
WHO	The World Health Organization

Acknowledgements

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has appointed an *ad hoc* group consisting of both VKM members and external experts to answer the request from the Norwegian Food Safety Authority. The report from the *ad hoc* group has been discussed and approved by VKM's Scientific Panel on Animal Feed. The members of the *ad hoc* group are acknowledged for their valuable contributions to this opinion.

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1. Background

The XyRex® formulations are antimicrobial agents with sodium chlorite as the active substance. The Norwegian Food Safety Authority has received a request to authorize XyRex® formulations for use in refrigerated sea-water (RSW) on board Norwegian fishing vessels for pelagic fish caught for production of fish meal/fish oil for use in animal feed. The Norwegian Food Safety Authority has defined the described use of XyRex® formulations as processing aid use. Legislation on processing aids in feed has not yet been harmonised in the EU. The European Parliament and Council Regulation (EC) No. 1831/2003 on additives for use in animal nutrition does not apply to processing aids. Substances not harmonised at the EU level is subject to national legislation.

The use of XyRex® formulations on fish for human consumption is not approved in Norway (letter from the Norwegian Food Safety Authority dated March 2, 2006, reference 04/49870).

2. Terms of reference

It is a premise that use of food processing aids should not pose a threat to health of humans or animals. If XyRex® formulations are used in RSW tanks, the products will not be rinsed off before the production of fish meal/fish oil for use in animal feed. The Norwegian Food Safety Authority has therefore in a letter dated May 18, 2006, with reference 2006/16028, requested The Norwegian Scientific Committee for Food Safety (VKM), Scientific Panel on Animal Feed, to assess the safety to humans and animals of the use of XyRex® formulations in RSW on board fishing vessels for pelagic fish.

The following specific questions were raised by the Norwegian Food Safety Authority:

- Can XyRex® be used in the RSW on board fishing vessels for pelagic fish caught for production of fish meal/fish oil for use in animal feed, without representing a health risk for the animals consuming the feed, the humans consuming animals fed on this feed, or for the environment?
- Since the XyRex®-treated fish are not rinsed before going into fish meal/fish oil production, is it to be expected that chlorine compounds originating from treatment with XyRex® are found in the fish meal/fish oil?
- Will the chlorine compounds in the XyRex® formulations react differently than chlorine compounds in the sea-water?
- Which chlorine compounds originating from XyRex® can be expected to be found in fish meal/fish oil, and will they represent a health risk for the animals consuming the feed, the humans consuming the animals being fed on this feed, or for the environment?
- Is it possible that dioxins are formed during drying of the fish meal made from this XyRex®-treated fish?
- Are specific limitations in the use of the XyRex® products necessary, i.e. in their concentrations, or is rinsing of the fish after treatment necessary, to ensure that the products do not represent a health risk for the animals consuming the feed, the humans consuming the animals being fed on this feed, or for the environment?

The Panel of Animal feed has focused this opinion on the toxicological evaluation of residues of sodium chlorite and sodium chlorate from the XyRex®-formulations. The amounts of these substances formed and transferred with the fish to the fish meal, fish meal-containing feed, and ultimately to the fish, meats, milk and eggs from animals eating the fish meal, are not known. Therefore, this evaluation is based on a worst-case scenario of transfer of the maximum amounts of these residues from the XyRex®-formulations, and the available information on theoretical transfer in each step from the RSW tanks on board fishing vessels into fish and animal feed and human foods. The likelihood of by-product formation from the specified use of the XyRex®-formulations has also been addressed.

The Panel of Animal feed has not evaluated the disinfecting activity claimed for the XyRex® products, nor the potential for development of bacterial resistance after use of the XyRex® products, since these questions were not asked by the Norwegian Food Safety Authority.

3. Health risk assessment

3.1. Risk assessment of component residues in the XyRex® products

According to the document "Documentation submitted in support of a request for use of XyRex® product range for the removal of microbial contamination in seafood", final draft, 29 November 2006, with the Appendices 1-7, received from XyRex® Ltd., Scotland, UK, a range of XyRex® formulations marketed for various uses, are to be evaluated. However, the XyRex® formulations P3/P3 Blue and P3 Plus/P3 Plus Blue are the products specified for use within the RSW system and in storage tanks on board fishing vessels for pelagic species, and only these formulations will be evaluated according to the request from The Norwegian Food Safety Authority.

The procedure for the manufacturing of XyBase, the main ingredient in the XyRex® formulations, as well as certificate of analysis/certificate of conformity to stated formulation, are supplied for the raw materials. Product specifications are given for the XyRex® formulations. Based on this information, the ingredients in the XyRex® formulations, as well as their manufacturing procedures, are of a quality sufficient for use in contact with food. The sodium chlorite concentration stated for final use is 12.5 ppm (12.5 mg/kg) in the XyRex® formulations used in RSW tanks.

The use of the XyRex® formulations will result in the release of five primary chlorine compounds; chlorite (ClO_2^-), chlorate (ClO_3^-), chlorous acid ($HClO_2$), chlorine dioxide (ClO_2) and chloride (Cl^-). Chlorous acid is a semi-stable intermediate that forms when sodium chlorite is acidified, and is essentially the chlorite ions and the hydrogen ions in equilibrium with a dissociation constant (pK_a) of 1.94 (1). In this case, according to XyRex® Ltd., the naturally produced volatile acids in degrading fish will lead to the acidification, and therefore additional supplement of acid is unnecessary. Chlorine dioxide will be rapidly reduced to chlorite and chloride, and to a lesser extent to chlorate. The ratio of chlorite to chlorate formed is approximately 7:3 (2). The exact proportion of each chlorine compound is dependent on the pH in the mixture. A guideline value has not been established for chlorine dioxide in drinking water because of its rapid hydrolysis to chlorite, and because the provisional guideline value for chlorite is adequately protective also for potential toxicity of chlorine dioxide (3). Therefore, sodium chlorite and sodium chlorate are the components in the XyRex® formulations that may cause concern for health risks.

This risk assessment will be limited to evaluations of residues of sodium chlorite and sodium chlorate from the XyRex® formulations in either fish (mostly farmed salmon) or domestic animals eating feed made from pelagic fish being stored with XyRex® in RSW tanks on board the fishing vessels, and for humans eating these fish and domestic animal meats, and milk and eggs. The potential for formation of by-products from components in the XyRex® formulations that may be of health risk will also be addressed. In addition, environmental effects of the use of XyRex® in RSW tanks on board the fishing vessels will be evaluated.

3.1.1. Sodium chlorite (CAS No. 7758-19-2)

3.1.1.1. Hazard identification and characterization

This description is based on an evaluation used for establishing The World Health Organization (WHO)'s guideline values for chlorite in drinking water from 2005 (3,4), The United States Environmental Protection Agency (EPA)'s toxicological review of chlorite from 2000 (5) and a document on disinfectants from The International Programme on Chemical Safety (IPCS) from 2000 (6). The readers are directed to these documents for further details.

Chlorite is rapidly absorbed from the gastrointestinal tract, and based on data in rats, it can be assumed that at least 35% of the initial dose is absorbed, with a half-time of 3.5 hours. Removal of chlorite from the blood is slow, with a half-time of 35.2 hours in rats. Approximately 85% of the dose recovered in urine of rats 0-72 hours after administration of a single gavage was in the form of chloride, the remaining 15% was chlorite. Urine is the primary route of excretion in rats.

Oral LD_{50} values in the range of 105-350 mg/kg body weight (bw) have been reported in rats, mice and guinea pigs. In salmoids, only data on rainbow trout (*Oncorhynchus mykiss*) has been found. In larval and adult rainbow trout, 96-hour LC_{50} values in water have been reported to be 106 and 149 mg/l, respectively (7). Animal toxicity databases for chlorite are fairly comprehensive and comprise of subchronic and chronic studies, reproductive and developmental studies, and toxicokinetic and mechanistic information. However, little or no information exist on various species of fish, including Atlantic salmon. Multiple animal studies have shown similar alterations in neurodevelopmental endpoints, such as brain weight and behavioural measures. The majority of these studies have used sufficient number of animals and employed routes of exposure (gavage and drinking water) relevant to human exposure. The majority of the developmental studies have utilized rats and have shown a fairly consistent definition of the no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) values. Reproductive effects occur at higher doses than the adverse developmental effects. The most consistent finding arising from exposure to chlorite is oxidative stress resulting in changes in red blood cells. However, clinical or toxicological alterations in hematological parameters also occur at higher doses than the adverse developmental effects.

Chlorite was negative in micronucleus test and a cytogenetic assay in mouse bone marrow cells *in vivo*. No human studies assessing carcinogenic potential of chlorite have been found. Chlorite was not shown to increase tumor incidences in rats or mice, and these studies were considered inadequate for assessing human carcinogenicity because the exposure was far less than a lifetime and because of other confounding factors, i.e. presence of virus in the rats, high mortality in control mice caused by fighting etc. The International Agency for Research on Cancer (IARC) concluded that chlorite was not classifiable as to its carcinogenicity to

humans (Group 3) (8), and EPA concluded similarly, i.e. that the compound was not classifiable as to human carcinogenicity (Group D) (9).

WHO has set a provisional guideline value for chlorite in drinking water of 0.7 mg/l (3,4). It is provisional because use of chlorine dioxide as a disinfectant may result in the chlorite guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection. A guideline value has not been established for chlorine dioxide because of its rapid hydrolysis to chlorite, and because the chlorite guideline value is adequately protective for potential toxicity from chlorine dioxide. The guideline value for chlorite was set on the basis of a tolerable daily intake (TDI) of 30 µg/kg bw/day based on a NOAEL value of 2.9 mg/kg bw/day identified in a two-generation study in rats, based on neurodevelopmental toxicity, i.e. lower startle amplitude and decreased absolute brain weight in the F1 and F2 generations, and altered liver weights in two generations, using an uncertainty factor of 100 (10 each for inter- and intraspecies variation). Eighty % of the TDI was allocated to drinking water, and 60 kg bw and a consumption of 2 litres/day were used in deriving the guideline value. EPA has set an oral reference dose (Rfd) of 30 µg/kg bw/day for chlorite or chlorine dioxide (5), using neurodevelopmental toxicity in the same two-generation rat study, and an uncertainty factor of 100.

3.1.1.2.Exposure characterization

In the present risk assessment of XyRex®, due to lack of more specific information, the Panel of animal feed has based the exposure calculations on a worst-case scenario where the maximum concentration of sodium chlorite in XyRex®, 12.5 ppm, used in RSW on board the fishing vessels catching the fish for fish meal/fish oil production, is transferred to the fish meal made from three different species of pelagic fish, as presented in Table 1. Further calculations of the transfer of sodium chlorite from the fish meal to the feed being eaten by either fish (farmed salmon) or domestic animals, which subsequently are consumed by humans, are presented in Table 2. The information in these tables represents the best qualified estimations the Panel of animal feed could make, based on available data from Fiskeriforskning, Bergen (personal communication with Øistein Høstmark) and Felleskjøpet Fôrutvikling, Trondheim (personal communication with Hallgeir Sterten and Kari Ljøkjel).

As can be seen in Table 1, the use of XyRex® in RSW on board fishing vessels catching the three different species of pelagic fish, blue whiting, herring and mackerel, contribute roughly 2.3, 4.3 and 4.3 mg sodium chlorite per kg fish meal, respectively. These figures are based on the assumptions that all the protein is transferred to the fish meal. Fat and water content in the fish and fish meal are not included in the calculations, since fat is extracted as fish oil and the water is evaporated. In further calculations, the concentration of sodium chlorite is set to 5 mg/kg fish meal as explained in Table 1.

Table 1. Calculation of sodium chlorite content from process water in the RSW tanks to the fish meal.

	Fish species		
Process stage	**Blue whiting**	**Herring**	**Mackerel**
Water in RSW tanks (%)	35 ±5[1]	55 ± 5	65 ± 5
Sodium chlorite from XyRex® in RSW tanks on board (ppm)	12.5	12.5	12.5
Unloading water (%)	6 ± 1	6 ± 1	6 ± 1
Sodium chlorite in water phase entering fish meal factory (ppm)	(12.5 x 4)/6 = 8.3[1]	12.5	12.5
Sodium chlorite (mg/kg fish)	8.3 mg/litre x 60 litre/ton fish = 0.5 mg/kg fish	12.5 mg/litre x 60 litre/ton fish = 0.75 mg/kg fish	12.5 mg/litre x 60 litre/ton fish = 0.75 mg/kg fish
Fish composition: Fat content (%)[2] Protein content (%)[2]	 5 21	 10-20 17.5	 20-30 17.5
Sodium chlorite (mg/kg fish meal)[3]	(0.5 mg/kg fish)/(0.210 kg meal/kg fish) = **2.3 mg/kg fish meal[4]**	(0.75 mg/kg fish)/(0.175 kg meal/kg fish) = **4.3 mg/kg fish meal[4]**	(0.75 mg/kg fish)/ (0.175 kg meal/kg fish) = **4.3 mg/kg fish meal[4]**

[1]Water is added during the unloading process to facilitate pumping of the blue whiting. Of the 50-70 litre water unloaded with the fish, 20 litres originated from added fresh water, i.e. 40 litres of approximately 60 litres is RSW.

[2]These are average values. There are seasonal variations in the fat content, but the protein content is more stable when calculated on a basis of fat free dry matter.

[3]Calculation is based on the estimate that all the protein in the fish is transferred to the fish meal. Fat and water contents in the fish and fish meal are not included in the calculations, since fat is removed as fish oil and the water is evaporated. Sodium chlorite and sodium chlorate are highly soluble in water; 64 and 100 g/100 g water, respectively (1). This means that chlorite and chlorate are insoluble in fish oil.

[4]In further calculations (**Table 2**), the concentration of sodium chlorite is set to **5 mg/kg fish meal**.

In the following estimations of intake of sodium chlorite from XyRex® in farmed salmon and domestic animals eating this fish meal-containing feed, the information given in Table 2 is used. Based on a daily intake of fish meal-containing feed, farmed salmon, pig, beef cattle, dairy cattle, chicken and turkey will be exposed to 12.5, 14.0, 2.1, 5.0, 15.0 and 10.4 µg of sodium chlorite/kg bw/day, respectively.

As a worst-case scenario, we calculated intake of sodium chlorite for humans from consumption of farmed fish and meats, or milk and eggs, from domestic animals being fed on feed containing fish meal from XyRex®-treated fish, assuming that all the sodium chlorite the fish and animals were exposed to were accumulating in their flesh, or transferred to the milk or eggs (Table 2). The best available data on human intake were used. Data from dietary surveys using semi-quantitative food frequency questionnaires were available for fatty fish, milk/milk products and eggs, and the mean and 95 percentile values from the surveys were used to represent average and high intakes, respectively. When such studies where not available, data from household surveys were used to indicate average intakes, and wholesales information were used to indicate high intakes. These two types of intake data are representing less precise and higher values than real intake compared with the dietary surveys using food frequency questionnaires.

Table 2. Content in the feed, and exposure to sodium chlorite for farmed salmon, pig, beef cattle, dairy cattle, chicken and turkey eating this feed, and for humans eating fish and meats, milk and eggs from these animals.

	Type of animal					
	Farmed salmon	**Pig**	**Beef cattle**	**Dairy cattle**	**Chicken**	**Turkey**
Percentage of fish meal in feed	20	10[1]	5	5	2-3	4-5
Sodium chlorite in feed (mg/kg feed)	1.0	0.5	0.25	0.25	0.15	0.25
Intake of feed/day (kg)	0.040-0.050	0.6-0.7	4-5	10	0.065-0.070	0.1
Body weight (bw) (kg)	4-5	25-30	600	500	0.7-0.8	2.4
Sodium chlorite exposures in the various fish and animals[2] (µg/kg bw/day)	**12.5**	**14.0**	**2.1**	**5.0**	**15.0**	**10.4**
Feed conversion ratio (kg feed/kg weight gain or kg feed/kg product)	1.1	1.7	3.5	1.0	1.6	1.8
Total accumulated[3] sodium chlorite in fish/meats/milk/eggs[4] (mg/kg)	1.10[5]	0.15[6]	0.88[7]	0.08[8]	0.24[9]	0.45[10]
Average human consumption of fish/meats/milk/(eggs) (kg/day)	0.021[11] (mean)	0.056[12]	0.038[13]	0.517[14] (mean)	0.009[15] (0.017[16] (mean))	0.002[17]
Average human sodium chlorite intake if all accumulated in the fish/meats/milk/(eggs)[18] (µg/kg bw/day)	**0.38**	**0.14**	**0.57**	**0.71**	**0.04 (0.07)**	**0.02**
High human consumption of fish/meats/milk/(eggs) (kg/day)	0.049[11] (95 percentile)	0.068[19]	0.053[20]	1.159[14] (95 percentile)	0.032[21] (0.042[16] (95 percentile))	0.008[22]
High human sodium chlorite intake if all accumulated in the fish/meats/milk/(eggs)[18] (µg/kg bw/day)	**0.90**	**0.1**	**0.80**	**1.60**	**0.13 (0.17)**	**0.06**

[1]Fed with fish meal only from 10 kg bw up to 30 kg bw, then fed without fish meal until 110 kg bw when slaughtered.

[2]Based on the highest value of intake and the lowest value for body weight in the ranges.

[3]The theoretical total amount of sodium chlorite in fish/meats/milk/eggs if all sodium chlorite in the fish-meal containing feed accumulated in the fish/meats or was transferred to milk or eggs.

[4]Fish/meats as such, or as processed products, i.e. as eaten for dinner as well as other meals. Milk and other products produced from milk (cream, sour cream, ice cream, yoghurt, cheese, margarine, butter), and hen eggs.

[5]Calculated as: Sodium chlorite in the salmon feed is 1 mg/kg. The feed conversion factor for farmed salmon is 1.1, therefore the salmon are administered 1 mg sodium chlorite/kg feed x 1.1 kg feed/kg salmon, which gives 1.1 mg sodium chlorite/kg in the salmon.

[6]Calculated as: Sodium chlorite in the pig feed is 0.5 mg/kg. The feed conversion factor for piglets is 1.7, and the piglets are only fed fish meal from body weight 10 to 30 kg (total 20 kg bw gain). During this period, 0.5 mg

sodium chlorite/kg feed x 1.7 kg feed/kg piglet, gives 0.85 mg sodium chloride/kg piglet. Total accumulation of sodium chlorite during this period is then 0.85 mg sodium chloride/kg piglet x 20 kg piglet, which gives 17.0 mg sodium chlorite. This amount of sodium chloride is divided by the slaughter weight of 110 kg, which gives 0.15 mg sodium chloride/kg slaughtered pork.

[7]Calculated as: Sodium chlorite in the beef cattle feed concentrate containing fish meal is 0.25 mg/kg. A feed conversion factor for beef cattle is estimated to 3.5 kg feed concentrate/kg weight gain. Therefore, the beef cattle are administered 0.25 mg sodium chlorite/kg feed x 3.5 kg feed concentrate/kg weight gain, which gives 0.88 mg sodium chlorite/kg in the beef.

[8]Calculated as: Sodium chlorite in the dairy cattle feed is 0.25 mg/kg. The feed conversion factor for dairy cattle is 1.0. The cows are administered 0.25 mg sodium chlorite/kg feed x 10 kg feed/day, which gives 2.5 mg/kg sodium chlorite per cow per day. Further calculation on sodium chlorite content in milk is based on a milk production of 30 kg/day per cow. 2.5 mg sodium chlorite per cow divided by 30 kg milk/day = 0.08 mg sodium chlorite per kg (= litre) milk.

[9]Calculated as: Sodium chlorite in the chicken feed is 0.15 mg/kg. The feed conversion factor for chicken is 1.6, therefore the chickens are administered 0.15 mg sodium chlorite/kg feed x 1.6 kg feed/kg chicken, which gives 0.24 mg sodium chlorite/kg in the chicken.

[10]Calculated as: Sodium chlorite in the turkey feed is 0.25 mg/kg. The feed conversion factor for turkey is 1.8, therefore, the turkeys are administered 0.25 mg sodium chlorite/kg feed x 1.8 kg feed/kg turkey, which gives 0.45 mg sodium chlorite/kg in the turkey.

[11]Calculated as mean or 95 percentile of intake in consumers only of fatty fish, i.e. fish with a fat content of >5 grams/100 g fish fillet (salmon, trout, halibut, mackerel, herring and eel), and included fatty fish products to spread on bread (10). It is assumed that farmed salmon is the main fatty fish consumed in Norway, and the only of these fish species being fed fish meal.

[12]Calculated as average intake of pork based on household surveys made by Statistics Norway (11).

[13]Calculated as average intake of beef based on household surveys made by Statistics Norway (11).

[14]Calculated as mean or 95 percentile of intake of milk and milk products (cream, sour cream, ice cream, yoghurt, cheese, (light) margarine, (light) butter), but not included all milk products used in cooking (12).

[15]Calculated as average intake of chicken (assuming 80% of intake of poultry is chicken) based on household surveys made by Statistics Norway (11).

[16]Calculated as mean or 95 percentile of intake in consumers only of hen eggs (not included all eggs used in cooking) (12).

[17]Calculated as average intake of turkey (assuming 20% of intake of poultry is turkey) based on household surveys made by Statistics Norway (11).

[18]A human body weight of 60 kg is used.

[19]Calculated by dividing an intake of 24.8 kg pork per person per year (2006) in Norway by 365 days per year (13).

[20]Calculated by dividing an intake of 19.2 kg beef per person per year (2006) in Norway by 365 days per year (13).

[21]Calculated by dividing an intake of 11.8 kg chicken per person per year (2006) in Norway by 365 days per year (14).

[22]Calculated by dividing an intake of 2.9 kg turkey per person per year (2006) in Norway by 365 days per year (14).

Consumers in Norway have an estimated average daily intake of approximately 21, 56, 38, 9 and 2 g of fatty fish (mostly farmed salmon), pork, beef, chicken and turkey meats, respectively (Table 2). Estimated average daily intakes of milk and eggs were 517 and 17 g, respectively (Table 2). Using these values for intake, we calculated average exposure values of humans to sodium chlorite of 0.38, 0.14, 0.57, 0.04, 0.02, 0.71 and 0.07 µg/kg bw/day from intake of farmed fish, pork, beef, chicken, turkey, milk and eggs, respectively (Table 2). High-consumers in Norway have an estimated daily intake of approximately 49, 68, 53, 32 and 8 g of fatty fish, pork, beef, chicken and turkey meats, respectively (Table 2). Estimated high daily intakes of milk and eggs were 1159 and 42 g, respectively (Table 2). Using these values for intake, we calculated high values for sodium chlorite exposure in humans of 0.90, 0.17, 0.80, 0.13, 0.06, 1.60 and 0.17 µg/kg bw/day from intake of farmed fish, pork, beef, chicken, turkey, milk and eggs, respectively (Table 2).

3.1.1.3.Risk characterization

Animal health
In the absence of available data indicating that fish (salmon) or domestic animals (pig, cattle, chicken and turkey) are significantly more sensitive to sodium chlorite than humans, the estimated exposures of these animal were compared to the human TDI value of 30 µg/kg bw/day. The TDI value was established by WHO for drinking water on the basis of neurodevelopmental toxicity, which should also be a relevant effect for animals. This TDI value is similar to the Rfd of 30 µg/kg bw/day for chlorite set by EPA.

Based on a daily intake of fish meal-containing feed, farmed salmon, pig, beef cattle, dairy cattle, chicken and turkey will be exposed to 12.5, 14.0, 2.1, 5.0, 15.0 and 10.4 µg of sodium chlorite/kg bw/day, respectively. Since these estimated exposures are all below the human TDI value of 30 µg/kg bw/day, no adverse effects on animal health would be expected from exposure to sodium chlorite from this use of XyRex® for treatment of fish being used for fish meal being included in animal feed.

Also for other XyRex® formulations used in connection with catching of pelagic fish, such as Ice Active and Spray-Ice, having a sodium chlorite concentration of 25 ppm (25 mg/kg), the estimated exposures (Table 2) would still be at or below the TDI value for sodium chlorite.

Human health
This evaluation was based on a worst-case scenario, i.e. that all the sodium chlorite the fish and animals were exposed to were accumulating in their meats, milk or eggs. We calculated average and high sodium chlorite intakes for humans from consumption of farmed fish and meats, or milk and eggs, from animals being given feed containing fish meal made from XyRex®-treated fish. The average values were 0.38, 0.14, 0.57, 0.04, 0.02, 0.71 and 0.07 µg/kg bw/day from intake of farmed fish, pork, beef, chicken, turkey, milk and eggs, respectively (Table 2). Using values for high intake, we calculated high sodium chlorite exposures for humans of 0.90, 0.17, 0.80, 0.13, 0.06, 1.60 and 0.17 µg/kg bw/day from intake of farmed fish, pork, beef, chicken, turkey, milk and eggs, respectively (Table 2).

All of these estimated exposure values, both based on average and high intakes, are well below the TDI value for sodium chlorite of 30 µg/kg bw/day. In reality, some of the sodium chlorite will have been depleted while in contact with the fish (up to 50% depletion after 30 seconds immersion of fish filets in XyRex®-formulations with 12.5 ppm sodium chlorite according to the information from XyRex® Ltd.). In addition, it is not likely that significant sodium chlorite will accumulate in the fish and meats, or milk and eggs, since it is excreted, primarily in the urine (as found for rats), which gives an even more conservative situation for humans.

Therefore, eating farmed fish and meats, or milk and eggs, from fish and domestic animals being given feed containing fish meal made from XyRex®-treated fish should not represent a health risk to humans. Even if overdosing of the fish should occur occasionally, no effects on human health are expected because of the uncertainty factor included in the estimation of TDI (i.e. 100), and since such an event is not likely to result in a daily increased exposure.

Also for other XyRex® formulations used in connection with catching of pelagic fish, such as Ice Active and Spray-Ice, having a sodium chlorite concentration of 25 ppm (25 mg/kg), the

estimated average and high exposure values for humans would still be well below the TDI value for sodium chlorite.

Conclusions
The estimated exposures of farmed fish and domestic animals to sodium chlorite in their fish-meal containing feed, as well as for humans having average and high intakes of fish and meats, or milk and eggs, from these animals, are all below the TDI value of 30 µg/kg bw/day set for sodium chlorite. Therefore, no adverse effects on fish or animal health, or human health, would be expected by exposure to sodium chlorite from the use of XyRex® formulations in RSW on board the fishing vessels catching fish being used for production of fish meal being included in fish and animal feed.

3.1.2. Sodium chlorate (CAS No. 7775-09-9)

3.1.2.1.Hazard identification and characterization

In beef cattle dosed with 62.5 or 130.6 mg/kg bw sodium[^{36}Cl]chlorate for three consecutive days, the radiochlorine absorption was 62-68% of the total dose with the major excretory route being urine (15). Parent chlorate was 65-100% of the urinary radiochlorine and chloride was the only other radiochlorine species present. Also in swine orally dosed with 20, 40 or 60 mg/kg bw sodium[^{36}Cl]chlorate for 30 hours, the elimination averaged 81.6-83.9% in urine and 1.1% across all doses in feces (16). Parent chlorate was always more than 97.4% in urine, and 39-77% in feces depending on the dose, the rest was chloride ion.

The toxicity database for chlorate is less extensive than that for chlorite. Oral LD_{50} values in the range of 185-8350 mg/kg bw have been reported in various mammals. Data on accidental poisonings indicate that the lethal dose to humans is about 230 mg/kg bw/day. The primary concern also with chlorate is oxidative damage to red blood cells.

Developmental toxicity (NTP Study TER97005), carcinogenicity studies and genetic toxicity studies (NTP Study TR-517) of sodium chlorate have now been completed by the National Toxicology Program (NTP) in U.S.A. (17). Female New Zealand White rabbits were dosed by gavage with 0, 100, 250, 500, 750 or 1000 mg/kg bw/day of sodium chlorate in a screening study, or with 100, 250 or 475 mg/kg bw/day of sodium chlorate in a developmental study, in both cases on gestational days 6 through 29, and terminated on gestational day 30 (17). Only transient changes in maternal food intake, urinary colour and/or output were noted at ≥100 mg/kg bw/day, but clear evidence of maternal toxicity was observed only at doses >475 mg/kg bw/day in the screening study. Sodium chlorate did not cause any significant treatment-related developmental toxicity in this study. Thus, the maternal and developmental toxicity NOAELs were greater than or equal to 475 mg/kg bw/day.

Groups of 50 male and 50 female F344/N rats were exposed to drinking water containing 0, 125, 1000 or 2000 mg/l sodium chlorate for 2 years (equivalent to average daily doses of approximately 5, 35 and 75 mg/kg bw/day for male rats, and 5, 45 and 95 mg/kg bw/day for female rats) (17). Survival of exposed rats was similar to that of the control groups. Mean body weights of all exposed groups were similar to those of the control groups throughout the study. Water consumption by exposed rats was generally similar to that of controls throughout the study. Serum concentrations of thyroxine and triiodothyronine were significantly reduced in 1000 and 2000 mg/l males and females on day 4, and in 2000 mg/l males and females at week 3. Serum concentrations of thyroid stimulating hormone were significantly increased in 1000 and 2000 mg/l males on day 4 and at week 3, in 1000 and 2000 mg/l females on day 4,

in 2000 mg/l females at week 3, and in 2000 mg/l males and females at week 14. All special study rats in the 1000 and 2000 mg/l groups had thyroid gland follicular cell hypertrophy at 3 and 14 weeks. There were positive trends in the incidences of thyroid gland follicular cell carcinoma in male rats, and of thyroid gland follicular cell adenoma or carcinoma (combined) in males and females. The incidences of thyroid gland follicular cell hypertrophy were significantly increased in all exposed groups of males and in 1000 and 2000 mg/l females. Thyroid gland focal follicle mineralization occurred in most 1000 and 2000 mg/l female rats. The incidences of hematopoietic cell proliferation in the spleen of 2000 mg/l males and bone marrow hyperplasia in 1000 and 2000 mg/l males were significantly greater than those in the controls.

Groups of 50 male and 50 female $B6C3F_1$ mice were exposed to drinking water containing 0, 500, 1000 or 2000 mg/l sodium chlorate for 2 years (equivalent to average daily doses of approximately 40, 80 and 160 mg/kg bw/day for male mice, and 30, 60 and 120 mg/kg bw/day for female mice) (17). Survival of exposed mice was similar to that of the control groups. Mean body weights of exposed females were generally less than those of the control groups after week 84 of the study. Water consumption by exposed mice was generally similar to that of controls throughout the study. There was a positive trend in the incidences of pancreatic islet cell adenoma or carcinoma (combined) in female mice. Thyroid gland follicular cell hypertrophy was significantly increased in 2000 mg/l females. The incidences of bone marrow hyperplasia were significantly increased in all exposed groups of females.

In summary, under the conditions of this 2-year drinking water study (17), there was *some evidence of carcinogenic activity* of sodium chlorate in male and female F344/N rats based on increased incidences of thyroid gland neoplasms. There was *no evidence of carcinogenic activity* of sodium chlorate in male $B6C3F_1$ mice exposed to 500, 1000 or 2000 mg/l. There was *equivocal evidence of carcinogenic activity* of sodium chlorate in female $B6C3F_1$ mice based on marginally increased incidences of pancreatic islet neoplasms. Exposure to sodium chlorate resulted in nonneoplastic lesions in the thyroid gland of male and female rats and female mice, bone marrow of male rats and female mice, and spleen of male rats. None of these newer studies justify a change in the TDI previously set (see below).

Sodium chlorate was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA104 or TA1535; all tests were conducted with and without exogenous metabolic activation (induced rat or hamster liver S9 enzymes) (17). *In vivo*, no increases in the frequencies of micronucleated normochromatic erythrocytes were seen in peripheral blood samples from male and female $B6C3F_1$ mice exposed to sodium chlorate in drinking water for 3 weeks (17).

In two recent studies, chlorate was detected in skeletal muscle, adipose tissue and internal organs of beef cattle and swine given oral sodium[^{36}Cl]chlorate (15,16). In the beef cattle, chlorate represented 28-57% of the total radioactive residues in skeletal muscle, the rest being chloride, whereas in liver, kidney and adipose tissues, chlorate ion represented a smaller percentage of the total residues (15). In the swine, chlorate concentrations in edible tissues ranged from 0.01-0.49 mg/kg, with residues in liver and skeletal muscle generally lower than those in kidney and adipose tissue (16). Chlorate was concentrated in thyroid tissues (7.7-25.4 mg/kg) relative to edible tissues. No evidence for chlorite was observed in excreta or in tissues. However, whether chlorate would be detected in fish muscle is not known.

WHO has set a provisional guideline value for chlorate in drinking water of 0.7 mg/l (3,4). It is provisional because use of chlorine dioxide as a disinfectant may result in the chlorate guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection. This guideline value was set on the basis of a TDI value of 30 µg/kg bw based on a NOAEL value of 30 mg/kg bw/day identified in a well-conducted 90-day study in rats, based on thyroid gland colloid depletion at the next higher dose, and using an uncertainty factor of 1000 (10 each for inter- and intraspecies variation, and 10 for the short duration of the study). Eighty % of the TDI was allocated to drinking water, and 60 kg bw and a consumption of 2 litres/day were used in deriving the guideline value.

3.1.2.2.Exposure characterization

The amounts of chlorate formed during use of XyRex® are lower than the amounts of chlorite, since it is not added as an ingredient in these products and is formed by degradation of chlorine dioxide in lower amounts than chlorite, i.e. in a ratio of approximately 3:7 (2).

3.1.2.3.Risk characterization

A TDI value for chlorate of 30 µg/kg bw/day has been set for drinking water, which is similar to the TDI for sodium chlorite. The level of chlorate present in contact with the fish in the RSW tanks, and therefore in the fish meal made from this fish, in fish meal-containing feed, and subsequently in fish or domestic animals, and ultimately in the human foods made from these animals, is less than for chlorite, as explained above. Since the risk characterization of chlorite concluded that the exposures of fish, domestic animals or humans were below the TDI value, and consequently that there were no health risks for fish or domestic animals, or for humans, from the specified use of the XyRex® formulations, the same conclusions are valid also for chlorate, having a similar TDI value.

Conclusions

The estimated exposures of farmed fish and domestic animals to sodium chlorate in their fish-meal containing feed, as well as for humans having average or high intakes of fish and meats, or milk and eggs, from these animals, are all below the TDI value of 30 µg/kg bw/day set for sodium chlorate. Therefore, no adverse effects on fish or animal health, or human health, would be expected by exposure to sodium chlorate from this use of XyRex® formulations in RSW on board the fishing vessels catching fish being used for production of fish meal being included in fish and animal feed.

3.2.Risk assessment of potential by-products formed after use of XyRex® formulations

3.2.1. By-products such as polychlorinated dioxins and furans

Polychlorodibenzo-*p*-dioxins (PCDD) and polychlorodibenzo-furans (PCDF) are formed from organic material in the presence of chlorine at temperatures between 250 and 450°C (18,19). Fish meal are made from fish cooked at 100°C. Since the fish meal used for animal feed and for human consumption are dried at a temperature below 130°C and 90°C, respectively (20), it is not likely that dioxins or furans are formed from the chlorine substances present in the fish meal from the use of XyRex® formulations. It is more likely that simpler chlorine compounds are formed than complex ones like dioxins and furans. In addition, only very small amounts of chlorine substances will be present in the fish meal (see below).

Conclusions
Because the temperatures used for cooking and drying during fish meal production are well below the temperatures where dioxins and furans are formed, the formation of these substances in this situation is unlikely.

3.2.2. By-products known from drinking water disinfected with chlorine dioxide or chlorite

The use of chlorine dioxide in drinking water disinfection has increased in later years because of concerns regarding formation of potentially harmful trihalomethanes and other chlorination by-products when using chlorine for disinfection, especially when organic material, such as humus, is present (6). As opposed to chlorine, which reacts mainly via oxidation and electrophilic substitution, chlorine dioxide reacts only by oxidation. This explains why it does not produce organochlorine compounds. Several studies showed that the total organic halogens formed with chlorine dioxide are 1-15% of what are formed with chlorine (6). The major inorganic chlorine dioxide by-products are chlorite and chlorate. The application of chlorine dioxide produces about 0.5-0.7 mg chlorite and 0.3 mg chlorate per mg chlorine dioxide (6). Chlorite ion is also produced when chlorine dioxide reacts with organic compounds. In contrast to chlorine treatment, chlorine dioxide generally forms reduced levels of halomethanes in drinking water, but can increase the levels of other potentially toxicologically important by-products (21,22). At a pilot plant in U.S.A., no halomethanes, but more than 40 different semivolatile organic disinfection by-products were detected after various chlorine dioxide treatments of raw river water, including maleic anhydrides and halopropanones (21). However, the concentration range was very low in this study, being 1-10 ng/l for semivolatile compounds, and around 0.05 mg/l for total organic halide compounds. No data has been found on how formation of by-products is affected when using chlorine dioxide directly on fish, where much more organic material is present, than when using it for disinfection of drinking water or swimming pools.

Chlorine dioxide does not oxidize bromide, present in sea-water, without sun light present. Therefore, chlorine dioxide from the use of XyRex® products added to sea-water in the RSW tanks, should not give rise to formation of bromoform or bromate (6).

Also, little is known about potential formation of by-products from reaction of chlorite or chlorate with organic materials. However, no chlorinated organics were detected after reactions of acidified sodium chlorite (ASC) with poultry carcasses (2).

The exact amounts of chlorine dioxide, chlorite and chlorate present together with the fish after use of XyRex® products are not known, and will probably vary with time because of their reactivity, and are depending on pH and temperature. Therefore, no exact calculations of by-product formation from the use of XyRex® products can be performed. Since the amounts of these compounds present with the fish are low, we regard any significant health risks from such by-products to be unlikely. However, further data might be needed to confirm that chlorinated compounds are not generated to a significant extent.

Conclusions
Since the amounts of chlorine compounds present with the fish are low, we regard any significant health risks from chlorination by-products to be unlikely. However, further data might be needed to confirm that chlorinated compounds are not generated to a significant extent from the use of XyRex® formulations.

3.2.3. By-product formation and effects on quality by reactions of components in the XyRex® formulations with proteins, fat and carbohydrates in the fish

The European Food Safety Authority (EFSA) has recently evaluated the use of acidified sodium chlorite (ASC) and chlorine dioxide on poultry carcasses (2) since these substances may potentially interact with either organic matter in solution or protein, fat and carbohydrate compounds giving rise to different reaction products. ASC is a combination of sodium chlorite and any acid generally approved in food. The principle of the XyRex®-formulations is similar to ASC, except that the producer claims that the natural low pH of the fish make the addition of an acid unnecessary. Therefore, similar reactions on protein, fat and carbohydrate compounds may take place in fish treated with XyRex® formulations as when using ASC. In theory, the quality of the fish meal and fish oil produced from XyRex®-treated fish may be affected.

The data reported by EFSA showed that ASC did not significantly affect the protein or fat content in poultry carcasses, except for some indication of oxidation of the skin (2), and no chlorinated organic by-products were formed.

Experimental results have shown that chlorine dioxide can readily react with amino acids, peptides, proteins and lipids. Chlorine dioxide reacts with free amino acids and dipeptides in solution giving rise to by-products. Reaction of chlorine dioxide with 21 amino acids and 3 peptides under laboratory conditions at pH 6 showed that only 2 amino acids (tyrosine and hydroxyproline) and the peptides produced by-products with mutagenic potential in the Ames *Salmonella typhimurium* assay using strains TA100 and TA98 with and without metabolic activation. With metabolic activation, the mutagenic activity was lower. Chemical by-product species responsible for this activity were not identified (23). By-products arising from the reaction of chlorine dioxide with L-tryptophan were also found to be direct-acting mutagens to the *Salmonella typhimurium* strains TA100 and TA98, and some fractions of the mutagenic reaction mixture also significantly increased the frequency of sister chromatid exchange in Chinese hamster ovary cells in the absence of activation (24).

However, chlorine dioxide treatment of poultry chiller water samples has been found not to induce significant levels of revertants in *Salmonella typhimurium* strain TA100 without metabolic activation (not tested with metabolic activation), even when tested at four times the level required for disinfection (25). Furthermore, organic extracts of Atlantic salmon and red grouper fillets treated with 20 and 200 mg/kg aqueous chlorine dioxide for 5 minutes did not show mutagenic activity in the *Salmonella typhimurium* strains TA98 and TA100 with and without activation (26). The reaction products in the treated aqueous solutions processed similarly did not show mutagenic activity either (26).

Chlorine compounds can readily react with lipids and be incorporated into free fatty acids as shown by model experiments using radiolabelled aqueous solutions of chlorine dioxide (27). Total susceptible fatty acids represent up to 50% of the total lipid content of poultry muscles and results show that the most susceptible are polyunsaturated fatty acids. However, the extent of incorporation of chlorine into lipids was shown to be very low. Chlorine dioxide is by and large less reactive with lipids than hypochlorous acid (27). Furthermore, no effects on protein or lipid contents were reported after treatment of Atlantic salmon and red grouper

fillets with 20, 40 100 and 200 mg/kg chlorine dioxide in brine (3.5% NaCl solution) for 5 minutes (28). Such treatments did not cause any obvious change in the fatty acid compositions of treated fishes, and only thiamin and riboflavin contents were lowered after treatment with chlorine dioxide in brine, but also in brine without chlorine dioxide, possibly due to a solubilization effect of salt on the vitamins.

The double bonds in the fatty acid moieties can undergo oxidation and addition in the presence of electrophiles, such as chlorine dioxide. The major reaction of chlorine dioxide is oxidation, rather than chlorination. Fatty acids in fish are more unsaturated than fatty acids in poultry, and therefore more easily oxidized than fatty acids in poultry carcasses (29). If the fatty acids in the fish treated with the XyRex® formulations are oxidized significantly, the quality of the fish oil produced from this fish may be affected.

Reactions of chlorine dioxide with aldehydes and ketones as well as carbohydrates have also been reported under laboratory conditions, giving rise to the formation of carbonyl compounds and oxidation reaction products, respectively (2). However, it appears that the amounts of carbohydrates and volatile aldehydes and ketones in poultry carcasses are too low to result in formation of significant levels of by-products of toxicological relevance. No data are available regarding carbohydrate content of fish.

Conclusions
Based on the somewhat limited data available on reactions of ASC and chlorine dioxide with poultry carcasses or fish, a significant formation of harmful, i.e. mutagenic, by-products from the use of the XyRex® formulations on fish is not expected. A negative effect on the quality of the fish oil, if substantial oxidation is taking place, can not be ruled out.

4. Environmental risk assessment

The use of XyRex® formulations results in the release of five primary compounds: chlorite (ClO_2^-), chlorate (ClO_3^-), and chlorous acid ($HClO_2$), chlorine dioxide (ClO_2) and chloride (Cl^-). However, as described above sodium chlorite and sodium chlorate are the main compounds formed, and the environmental risk assessment of the use of XyRex® formulations will therefore be limited to these two compounds.

Chlorite has been shown to be relative non-toxic to brown algae, but much more toxic to green and blue-green algae and bacteria (30), with a reported LOEC of 0.08 mg/l in a green algae. In freshwater, chlorite LC_{50} in rainbow trout (*Oncorhynchus mykiss*) is reported to be 208.76 mg/l (31). In another study, chlorite 96-hour LC_{50} values for larval and adult rainbow trout were 106 and 149 mg/l, respectively (7), indicating that larvae are more sensitive than adult rainbow trout.

Risk posed by chlorate has been assessed on aquatic organisms, and the geometric mean $E(L)C_{50}$ values for both freshwater and marine species were 38 5883 mg/l, 563 mg/l, 2442 mg/l, 3185 mg/l for microorganisms, microalgae, invertebrates and fish, respectively (32). Marine macro red algae were insensitive to chlorate, whereas marine macro brown algae (e.g., Fucus sp.) appeared to be exceptionally sensitive to chlorate. In macro brown algae, adverse long-term effects were reported in concentrations as low as 0.015 mg/l (32). NOEC after 6 months was reported to be approximately 0.005 mg/l (30,32). Chlorate has also been shown to

be toxic to marine micro algae, particularly in nitrate limited waters, although the sensitivity appears to differ between species (33).

The possible ecological impacts of XyRex® are related to the release of water containing sodium chlorite and sodium chlorate into the sea, and in particular with respect to marine brown algae, and possibly also green algae. Harmful effects due to exposure may occur during unloading of catchments if RSW containing these compounds leaches or is intentionally discharged into the sea. If the concentration in released water is high, local effects on marine biota, in particular on brown algae, and possibly also green algae, may occur. To avoid possible local effects on marine algae, the concentrations of chlorate and chlorite in the marine environment should be below 0.015 mg/l and 0.08 mg/l, respectively. Release of RSW in harbour areas is forbidden by law in Norway and will be reported to the police (Norges Sildesalgslag (personal communication with Kenneth Garvik), Karmsund Fiskemel AS (personal communication with Ståle Stonghaugen) and Egersund Sildeoljefabrikk AS & Co (personal communication with Olaf Unhammer)). Hence, the RSW is released from the fishing vessels in open sea during transport. Therefore, the concentrations of sodium chlorite and sodium chlorate in the sea-water will rapidly be diluted around the release point, and are not likely to have any adverse effects, and therefore do not pose an environmental risk.

Conclusions
Release of RSW in harbour areas is forbidden by law in Norway. The concentrations of sodium chlorite and sodium chlorate in RSW being released from the fishing vessels to open sea during transport will rapidly be diluted around the release point, and are therefore not likely to have any adverse effects. The specified use of XyRex® formulations in RSW on board fishing vessels is therefore not expected to be of significant environmental concern.

5. Lack of and uncertainties in the data

5.1. Estimation of exposure to the components in XyRex®

In this risk assessment, the exposure calculations are based on a worst-case scenario where the maximum concentrations of sodium chlorite and sodium chlorate in the XyRex® formulations used in RSW tanks on board the fishing vessels catching the fish for fish meal production are transferred to the fish meal, and further transferred in the fish meal-containing feed to either farmed fish or domestic animals. Thereafter, human exposures through consumption of meats from the farmed fish and domestic animals, or from milk and eggs, are based on worst-case calculations where all the sodium chlorite and sodium chlorate that were estimated to be fed to the fish and animals through fish meal, are assumed to accumulate in their flesh or transfer into milk and eggs. In all the steps leading to the final exposure values (Tables 1 and 2), data were collected from available sources in Norway, i.e. from Fiskeriforskning, Bergen (personal communication with Øistein Høstmark) and Felleskjøpet Fôrutvikling, Trondheim (personal communication with Hallgeir Sterten and Kari Ljøkjel).

Obviously, there are uncertainties in the final calculated exposure values, since there are some variation and uncertainties in all of these data. However, in reality, a significant amount of the sodium chlorite in the XyRex® formulations will be depleted during the disinfection process and not end up in the fish meal and hence not in the feed. Furthermore, both sodium chlorite and sodium chlorate will to a large extent be excreted rather than accumulated in the meats of

fish and animals, or transferred into milk and eggs. Therefore, the real exposure values will in reality be lower than the values estimated here.

There are additional uncertainties in the data for human intake of the various types of meats in Norway. However, also the intake estimated on the basis of wholesales data, being higher than the real consumption, gave human exposure values below the TDI values.

Therefore, the Scientific Panel of Animal Feed finds that the present risk assessment is conservative and valid, since the potential errors are all on the side of caution.

5.2. Contribution to the exposures from other sources

Potential exposures from other sources are not included in the risk characterizations of sodium chlorite, sodium chlorate and by-products above. The major route of exposure to sodium dioxide, sodium chlorite and sodium chlorate is through disinfection of drinking water (3,4). The potential by-products that may be formed by the use of XyRex® are also mainly formed by disinfection of drinking water. Chloride dioxide, sodium chlorite and sodium chlorate may also occur in foodstuffs as a results of their use in flour processing, as a decolorizing agent for carotenoids and other natural pigments (chloride dioxide), and as bleaching agents in the preparation of modified food starch (sodium chlorite). Chloride dioxide is also used as a bleaching agent for cellulose, paper pulp and oils, and for cleaning and detanning leather. Sodium chlorite is also used as a bleaching agent in production of paper and paperboard products, including food packaging materials, and in textiles and straw products, as well as in the manufacture of waxes, shellacs and varnishes. Sodium chlorate is used in the preparation of chlorine dioxide, in the manufacture of dyes, matches and explosives, for tanning and finishing leather, and in herbicides, fungicides, defoliants and desiccants in agriculture.

Data for potential exposures from other sources was available only for sodium chlorite. The levels of chlorite in drinking water when chlorine dioxide is used for disinfection were reported in one study to range from 3.2 to 7.0 mg/l (3,4). These levels contribute substantially more than the contributions from the use of XyRex® formulations as estimated in this risk assessment. However, chlorine dioxide, which generates sodium chlorite and sodium chlorate, is not used for disinfection of drinking water in Norway at present, and therefore do not add to the total exposure either of domestic animals or humans.

5.3. Exposure to mixtures of compounds

Evaluation of potential additive or synergistic effects of exposures to multiple compounds simultaneously has not been performed in this risk assessment.

6. Conclusions

- The use of the XyRex® formulations with a sodium chlorite content of 12.5 ppm will mainly result in the release of sodium chlorite and sodium chlorate, which therefore are the residual components in the XyRex® formulations that may cause concern for health risks. The estimated exposures of farmed fish and domestic animals to sodium chlorite and sodium chlorate through their fish-meal containing feed are all below the TDI value of 30 µg/kg bw/day set for both sodium chlorite and sodium chlorate. Therefore, no adverse effects on fish or animal health would be expected from exposure to sodium chlorite and sodium chlorate from the use of XyRex® formulations in RSW on board fishing vessels catching fish being used for fish meal being included in fish and animal feed.

- The intakes of sodium chlorite and sodium chlorate for humans from consumption of farmed fish and meats, or milk and eggs, from domestic animals being fed on fish meal from XyRex®-treated fish were estimated assuming the worst-case scenario that all the sodium chlorite and sodium chlorate the fish and animals were exposed to were accumulating in their meats, milk and eggs. These estimated average and high exposures to farmed salmon, pork, beef, chicken and turkey meats, or milk and eggs, are well below the TDI value for both sodium chlorite and sodium chlorate of 30 µg/kg bw/day. In reality, a significant amount of the sodium chlorite in the XyRex® formulations will be depleted during the disinfection process and not end up in the fish meal and thereafter in the feed, and both sodium chlorite and sodium chlorate will to a large extent be excreted rather than accumulated in the meats of fish and animals, which gives an even more conservative exposure situation for humans.

- Because the temperatures used for cooking and drying during fish meal production are well below the temperatures where dioxins and furans are formed, the formation of these substances in this situation is unlikely. Also, since the amounts of chlorine compounds present with the fish are low, we regard any significant health risks from chlorination by-products to be unlikely. However, further data might be needed to confirm that chlorinated compounds are not generated to a significant extent from the use of XyRex® formulations. Based on the available data on reactions of ASC and chlorine dioxide with proteins and lipids in poultry carcasses or fish, a significant formation of harmful, i.e. mutagenic, by-products from the use of the XyRex® formulations on fish is not expected. A negative effect on the quality of the fish oil, if substantial oxidation is taking place, can not be ruled out.

- Release of RSW in harbour areas is forbidden by law in Norway. The concentrations of sodium chlorite and sodium chlorate in RSW being released from the fishing vessels to open sea during transport will rapidly be diluted around the release point, and are therefore not likely to have any adverse effects. The specified use of XyRex® formulations in RSW on board fishing vessels is therefore not expected to be of significant environmental concern.

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