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Genome-edited salmon: a sustainable and socially acceptable solution to aquaculture?

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Abstract | Sammendrag

The Norwegian Atlantic salmon farming industry is halted by challenges related to environmental impact and fish welfare. Some of the issues have been suggested solved by the use of novel genome editing technologies, such as CRISPR, which allows for targeted mutations and speeding up fish breeding. For successful introduction, applications of the technology need to be socially acceptable and contribute to sustainability. In this dissertation, I study the technological potential and challenges, the sustainability issues, and conditions for social acceptance of introducing CRISPR in salmon farming, in three papers, respectively.

In paper I, a systematic literature review was conducted to identify and categorize publications that have used genome editing in aquaculture finfish species. The search was designed according to relevant PRISMA elements. Results shows that a wide variety of aquaculture species have been used, salmonids being the second most studied group, with a broad specter of potential for future application in aquaculture such as sterility, disease resistance and increased growth.

Paper II and III are both based on a qualitative study of semi-structured stakeholder interviews and citizen focus group interviews. The interviews were conducted in video calls and included three main topics: the salmon as an animal, genome editing, and sustainability. For paper II, considerations and conditions related to aquaculture, sustainability and genome editing were identified and merged with data from an analysis of international and national policy and strategy documents, to inform a biosphere-based sustainability assessment framework.

For paper III, general considerations, and conditions for social acceptance of genome-edited salmon were identified. Main finding where that across all interviews, considerations to the wild salmon viability and the farmed salmon welfare, are widely shared and seems to be of main concern to the study participants. Further, several conditions to the industry and products were raised, such as unintended consequences being unacceptable, and the editing must contribute to improve welfare above increasing profit.

The papers show that there are potential applications of genome editing under research which might be considered socially acceptance and sustainable for salmon farming. However, this seem to depend on social acceptance to the salmon farming industry in general, and on genome editing being applied in concert with other measurements that improve salmon health and welfare, and that reduces environmental effects.

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Norsk oppdrett av atlanterhavslaks har store utfordringer knyttet til miljøpåvirkning og fiskevelferd. Noen av problemene har blitt foreslått løst ved bruk av nye genredigeringsteknologier, slik som CRISPR, som gir mulighet for målrettede mutasjoner og å fremskynde avlsprosesser. For vellykket introduksjon må anvendelser av teknologien være sosialt akseptable og bidra til bærekraft. I denne avhandlingen studerer jeg det teknologiske potensialet og utfordringene, bærekraftsspørsmålene og betingelsene for sosial aksept ved å introdusere CRISPR i lakseoppdrett, i henholdsvis tre artikler.

I artikkel I ble det utført en systematisk litteraturgjennomgang for å identifisere og kategorisere publikasjoner som har brukt genredigering i fiskearter også brukt i akvakultur. Søket ble utformet i henhold til relevante PRISMA-elementer. Resultatene viser at flere akvakulturarter har blitt brukt, laksefisk er den nest mest studerte gruppen, og det foreligger et bredt spekter av potensial for fremtidig bruk i akvakultur, slik som sterilitet, sykdomsresistens og økt vekst.

Artikkel II og III er begge basert på en kvalitativ studie med semistrukturerte intervjuer med interessenter til oppdrettsnæringen samt fokusgrupper med norske innbyggere. Intervjuene ble gjennomført i videosamtaler, og inkluderte tre hovedtemaer: laksen som dyr, genredigering og bærekraft. I artikkel II, ble betraktninger og betingelser knyttet til akvakultur, bærekraft og genredigering identifisert og slått sammen med data fra en analyse av internasjonale og nasjonale policy- og strategidokumenter, for å informere et biosfærebasert rammeverk for bærekraftsvurdering.

I artikkel III ble mer generelle betraktninger og betingelser for sosial aksept av genredigert laks identifisert. Hovedfunn er at hensynet til villaksens levedyktighet og oppdrettslaksens velferd er et hovedanliggende for studiedeltakerne. Videre ble flere betraktinger og betingelser til industrien og produktene belyst, som at utilsiktede konsekvenser ikke er akseptable, og genredigeringen må bidra til å forbedre velferden fremfor å øke profitt.

Artiklene viser at det er potensielle anvendelser av genredigering under forskning som kan anses som sosial akseptable og bærekraftige for lakseoppdrett. Likevel ser det ut til at dette vil være avhengig av sosial aksept for lakseoppdrett generelt. Videre er det viktig at genredigering kombineres med andre løsninger som forbedrer laksens helse og velferd og reduserer miljøeffekter.

Abbreviations

CRISPR	Clustered Regulatory Interspaced Short Palindromic Repeats
GTA	Gene Technology Act
GM	Genetic Modification
GMO	Genome Modified Organism
KO	Knock-Out [of genes following genome editing]
LMO	Living Modified Organism
MN	Mega Nucleases
NBAB	Norwegian Biotechnology Advisory Board
NEA	Norwegian Environment Agency
PAM	Protospacer Adjacent Motif
PRISMA	Preferred Reporting Items for Systematic and Meta-Analyses
SDN	Site-Directed Nuclease
SLO	Social License to Operate
TALEN	Transcription Activator-Like Endonucleases
WT	Wild Type [control organism in experiment]
ZFN	Zinc Finger Nucleases

List of tables

List of figures

List of papers

I Blix, T. B., Dalmo, R. A., Wargelius, A., & Myhr, A. I. (2021). Genome editing on finfish: Current status and implications for sustainability. *Reviews in Aquaculture*, 13(4), 2344-2363. https://doi.org/10.1111/raq.12571

II Blix, T. B., & Myhr, A. I. (2023). A sustainability assessment framework for genome-edited salmon. *Aquaculture*, 562, 738803. https://doi.org/10.1016/j.aquaculture.2022.738803

III Blix, T. B., Winther, H., Myhr, A., Myskja, B., Holm, L. Social acceptance of CRISPR in salmon farming: what is at stake? (*submitted manuscript*)*

Contributions	Paper I	Paper II	Paper III
Concept and idea	TB, AM, RD	TB, AM	TB, HW, BM, AM, LH
Study design and methods	TB, AM, RD, AW	TB, AM	TB, HW, BM, AM, LH
Data gathering and interpretation	TB, AM	TB, AM	TB, HW, LH
Manuscript preparation	TB, AM, RD, AW	TB, AM	TB, HW, BM, AM, LH

*Blix and Winther contributed equally to the paper. The paper will therefore also be used in Winther´s doctoral thesis.

The Co-author statement is attached in Appendix 1.

All references including legal documents, reports and web resources are cited according to the issuer (e.g., legal authority) or author when available, and listed jointly under References. This is to align the style with that of papers I-III.

Cover photo: Torill Blix

Table of Contents

Introduction: scope of the thesis

Climate change and biodiversity loss are challenging global food production systems (Pörtner et al. 2021, 2022). Reciprocally, food systems are major contributors to these issues through negative environmental effects (Halpern et al. 2022). This stresses the need to change our food systems through more responsible management of natural resources (EC 2020, p. 7). Seafood has the potential to contribute to solving these issues because producing and harvesting foods from the ocean and water systems has reduced environmental effects compared to terrestrial animal protein (BFA 2021; Bianchi et al. 2022). Farming aquatic animals in aquaculture allows for increased food production while avoiding over-exploitation of wild aquatic species. Between the 1990s and 2020, total global aquaculture (inland and marine) production increased from 21,8 to 87,5 million tons (FAO 2022, p. 3). One of the species currently dominating *marine* aquaculture is Atlantic salmon (*Salmo salar,* from here: salmon), with Norway as the largest salmon producer (FAO 2022, p. 43, 97). This production is challenged by ecological impact and animal welfare issues. Escaped farmed salmon may negatively impact endangered wild salmon stocks (Thorstad et al. 2022) and disease and treatment thereof are reducing fish health and welfare (Sommerset et al. 2022). Ever since the beginning of salmon farming in Norway in the 1960s, major efforts have been put into adapting the salmon to its rearing conditions through selective breeding (Thodesen & Gjedrem 2006), and the most recent solution proposed is to use genome editing (Wargelius 2019) – a novel tool for changing and modifying DNA (Doudna & Charpentier 2014). Genome editing is the collective term for several different technologies where nucleases guided by RNA templates make double stranded cuts in DNA, and endogenous cellular repair systems repair the cut, generating a mutation at the desired loci. The most commonly used genome editing technology is Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR). This technology holds the potential for speeding up selective breeding of fish such as salmon, by enabling selective targeting of specific genes and either removing, enhancing, or regulating them, thereby changing specific traits of the animal. Applying such novel and disruptive technologies in aquaculture arguably calls for thorough investigation of technological, sustainability and social benefits and challenges (Myskja & Myhr 2020). Genome-edited organisms are currently considered to be genome modified organisms (GMOs) in the EU (Court of Justice of the European Union 2018), thus in Norway as well. In Norway, risk assessment of the effect on human health and the environment as well as non-safety assessment (Zetterberg & Björnberg 2017) of ethical

justifiability, societal acceptability and sustainability are required prior to acceptance of GMOs (Ministry of Environment 2005a).
In this thesis, I generate new knowledge suitable to answer the question: Is **genome-edited salmon a sustainable and socially acceptable solution to aquaculture**? This is explored in papers **I-III**, by addressing the sub-questions:

I What changes through genome editing are feasible now, and in the future, contributing to more sustainable and efficient salmon production? (Blix et al. 2021)

II What are the sustainability issues raised and how can genome-edited salmon be assessed for its contribution to sustainability? (Blix & Myhr 2023)

III How do representatives of the public and salmon farming stakeholders evaluate genome editing of salmon, and what kind of genome editing, if any, do they find acceptable? (Blix, Winther, Myskja, Myhr & Holm, *submitted manuscript*)

In paper **I**, my co-authors and I review what genes, traits and species have been targeted by genome editing thus far in research on a global scale, and what the prospects for future use are. We hypothesized that the technical possibilities of genome editing in salmon have not been fully explored, and while the research is innovative in using genome editing as a tool in applied and basic research on fish genetics and biology, it could also be useful in breeding of aquaculture species. We found that the CRISPR tool is already widely applied in research on aquaculture species. What is more, we found that Norway is one of the main countries researching in this field. Salmon is the only used species in these Norwegian studies, but several different traits and genes are targeted.

In paper **II,** we present a novel framework for a sustainability assessment of genome-edited salmon where the biosphere is prioritized. Stakeholder interviews and citizen focus groups supplemented with a document analysis are used to inform the content and structure of the assessment. We explore how sustainability is defined on a global scale, and in Norwegian aquaculture, hypothesizing that sustainability is an important criterion amongst stakeholders and citizens, but conceptualization differs between stakeholders and among citizens. We identified perspectives on sustainability concerns regarding aquaculture held by different stakeholder participants and among citizens, in addition to perceptions of sustainable development. The framework consists of topics and control questions considering the biosphere, society and the economy, in a hierarchal list.

In paper **III,** the main aim was to determine what the conditions are for social acceptance among stakeholders and citizens, and we asked what is at stake if we introduce genome editing in salmon farming. We used the same qualitative interview material as in paper II and identified that people´s considerations and conditions for use are mainly related to the genome-edited fish product, rather than the technology. Still, some reservations towards the technology were found, such as concerns about unintended consequences of genome editing. Applications that can reduce environmental impact and improve animal welfare are found to be more acceptable than applications which might increase impaired welfare and only benefit the salmon farming industry.

This thesis provides the context and theoretical background, as well as a chronological description of the methodological approaches and summaries of the main results from all three papers. In the end, I discuss the papers jointly to show how they together answer the thesis´ main research question. Exploring the three sub-questions requires input from different perspectives, and the work therefore takes an interdisciplinary approach, spanning from biotechnology into sustainability science and social science.

1 Background and theory

This section gives a detailed and theoretical background and the context for papers I-III. I first describe the discovery of the CRISPR technology and relevant GMO legislation. Then I turn to the industry in question – salmon farming in Norway, its history, and current challenges, which is closely associated to wild salmon. Finally, I elaborate on how sustainable development has been and is understood, and what have been and are considered to be conditions for the social acceptability of gene technologies in food production.

1.1 Genome editing and CRISPR in animals

Genetic modification (GM) technology emerged in the 1970s, where segments of DNA were moved between and within species, inserted into organisms or their cells, *in vitro* or *in vivo*. Transgenesis is when there is a transfer of genetic material between species, while cisgenesis is when genetic material is transferred within a species. In GM of animals, DNA can for example be inserted directly by a microneedle into in vitro fertilized zygotes or by transfection of embryonic stem cells, and a non-transgenic female is used to obtain the resulting transgenic offspring. The offspring would be either carrying or not carrying (more or less of) the inserted DNA segment at random locations in its DNA. A chimera is an organism which carries the modification in some, but not all cells, and crossing such GM chimeras could yield fully GM offspring. In GM, the placement of the DNA segment is random which makes detection of successful mutagenesis challenging, and there is also potential for disrupting other genetic features, for example if it is located in another gene, or regulator (Snustad & Simmons 2012, p. 463-464). GM has been applied in the breeding of several different crops (ISAA 2022), while the only GM animal commercially available as food is the AquAdvantage salmon (FDA 2022; USDA n.d.; Waltz 2017). This transgenic salmon possesses a growth hormone gene from Chinook salmon (*Oncorhynchus tshawytscha*), and a gene regulator from ocean pout (*Zoarces americanus*) (FDA 2022), which allows it to continuously grow and reach market size faster than conventionally bred salmon (Waltz 2017). Other ways of making changes in the genetic material of animals are chemical mutagenesis and triploidization, used to generate random mutations or introduce extra chromosome pairs. According to Norwegian legislation, such organisms are not GMOs.

Genome *editing* is another alternative to GM which includes different technologies derived from various natural cellular systems: meganucleases (MN) from microbial mobile genetic elements, zinc finger nucleases (ZFN) from transcription factors of eukaryotic cells, transcription activator-like effector nuclease (TALEN) from bacteria *Xanthomonas*, and CRISPR from widespread bacterial adaptive immune systems (Agapito-Tenfen & Wikmark 2015; Gaj et al. 2013; Hsu et al. 2014). The nucleases recognize a specific site of a genetic sequence, where they attach and make a double-stranded break (DSBs). The break is then approached by the intracellular DNA repair mechanism which initiates either the error-prone non-homologous end-joining (NHEJ) or homology-directed repair (HDR) (Agapito-Tenfen & Wikmark 2015; Hsu et al. 2014). NHEJ implies that proteins bind to the open DNA ends and facilitate the binding of repair proteins that join the ends, which leads to the insertion or deletion of one or more nucleotides where the break was made (site-directed nuclease-1 (SDN-1). HDR implies recombination with homologous arms from an exogenous DNA template, thus insertion of a small or large sequence (SDN-2 or SDN-3) (Hsu et al. 2014). Genome editing techniques thus allow for either the deletion, insertion, or substitution of genetic material in a cell's genome, transcripts or epigenetic elements (Hsu et al. 2014). A schematic representation of genome editing is shown in Figure 1. The focus of this thesis is the CRISPR system, and I will therefore not describe MN, ZFN or TALEN in more detail.

Even though CRISPR is a tool only recently applied in practice (Jinek et al. 2012), it has been a known concept since 1987. While studying the genome of *Escherichia coli,* Ishino et al. (1987) discovered 29 nucleotide repeats downstream of a gene. The research community found the repeats to be unexpected, as repetitive elements most often appear in tandem. These 29 nucleotide repeats were interspaced with five 32 nucleotide non-repetitive sequences. In 2002, the acronym CRISPR was suggested to describe this bacterial phenomenon (reviewed in Hsu et al. 2014), and in 2007 the first study confirmed the biological function of CRISPR (Barrangou et al. 2007). They found that the sensitivity of bacteria to bacteriophages correlated to the content of CRISPR1 loci in the bacteria genome, also in comparison to non-resistant parental strains. The study also showed that different bacteria strains exposed to the same bacteriophage subsequently contained more spacers inserted than wild type (WT, the control) equivalents, and that these spacers were also found in the genomic material of the phage. The conclusion was that the CRISPR systems are prokaryotic *immune defense systems* targeting viruses (Barrangou et al. 2007). The CRISPR systems´ functions differs between three different types (I-III), but generally, the CRISPR systems are activated through three phases (reviewed in Hsu et al. 2014 and Terns & Terns 2011):

i) **Adaptation**, when bacteria holding the CRISPR systems in their genome are attacked by a virus, a protospacer from the foreign DNA inserted from the bacteriophage is integrated in the CRISPR locus of the bacteria

ii) **CRISPR-RNA generation**, transcribed and matured CRISPR-RNA fragments are attached to Cas proteins which are then termed effector complexes

iii) **Silencing of foreign DNA**, the CRISPR-RNA forms base-pairing with a sequence in foreign DNA or RNA depending on the position of a protospacer adjacent motif (PAM) (target, recognition), thus *guiding* the Cas nuclease to the correct locus where the Cas nuclease cleaves the targeted sequence

Subsequently, when a new attack has occurred, new spacers are integrated from the bacteriophage genetic material, which further generates resistance towards that particular phage in future attacks (Barrangou et al. 2007). This makes the CRISPR systems learning-based systems, or a "genetic memory bank of past invasions and a source of small invader-targeting RNA" (Terns & Terns 2011, p. 2).

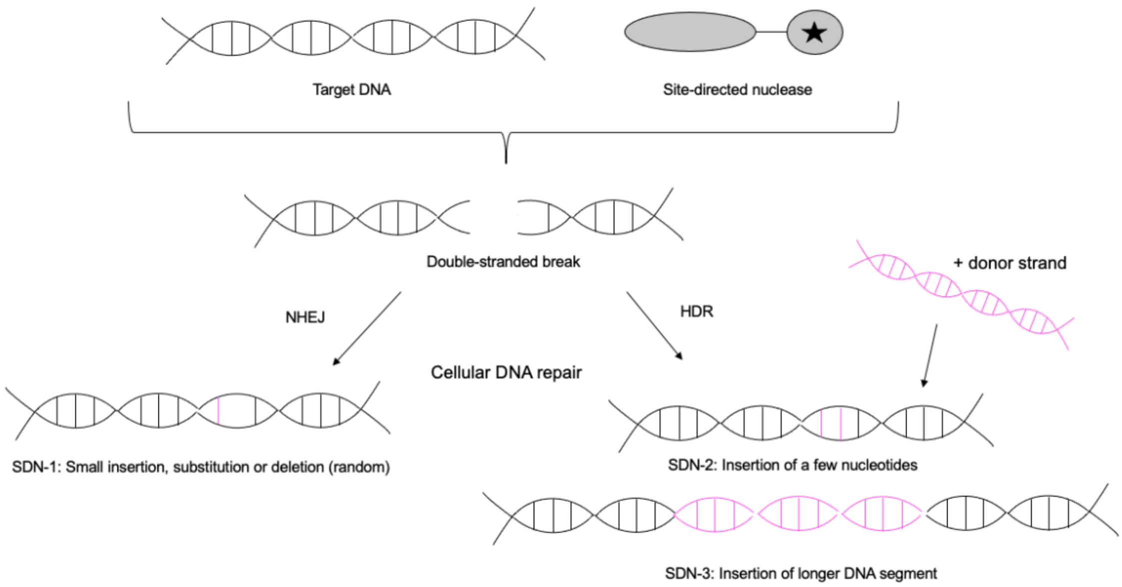

Figure 1 A simplified schematic representation of site directed nuclease activity. Subsequent to targeting, the nuclease makes a double-stranded cut in the DNA strand, which triggers cellular repair mechanisms. If no donor DNA is present, the repair is conducted by non-homologous end-joining (NHEJ), which leads to nucleotide deletion, substitution or insertion (SDN-1). Alternatively, with donor DNA present, homologous-directed repair is triggered, which leads to insertion of a few (SDN-2) or larger DNA segment (SDN-3). The illustration is modified from Agapito-Tenfen and Wikmark (2015).

Once the biological role of CRISPR was revealed, efforts were invested to turn the biological phenomenon into practical application. The most used Cas protein is the CRISPR/Cas9 endonuclease (Pacesa et al. 2022). Jinek et al. (2012) found that it is possible to "program" the Cas9 RNA to be specific to the site to be cleaved. By designing a dual tra-CRISPR-RNA and CRISPR-RNA strand, the CRISPR system can target any DNA sequence for cleavage, as long as the target site is in proximity to a guanine dinucleotide (GG), following the bacterial system where GG is the crucial part of the PAM sequence (Jinek et al. 2012). More recently, it has also been shown that some Cas9 enzymes are able to target and cleave not only DNA, but also RNA (Strutt et al. 2018). Genome editing is considered more specific than GM methods. Still, there are technical challenges such as *off-target* mutations – when the nuclease makes a cut outside the intended target site. The CRISPR/Cas9 system can target a sequence length of 20 nucleotides (Jinek et al. 2012; Zhang et al. 2016). The gRNA might target DNA at a similar locus to the one intended by design if there are 5 or less nucleotides mismatching this other segment (Kuscu et al. 2014). This reduces the mutation success and is potentially a safety concern in any application (Okoli et al. 2021; Pacesa et al. 2022). Still, such off-target events depend on the position of the mismatch, and further the requirements for the CRISPR system to not just target, but also make a cut. This is currently under investigation (Pacesa et al. 2022). Other technical challenges remain to be solved. These are more extensively described in paper I and Okoli et al. (2021). The delivery method for the CRISPR system into cells is also under constant optimization, and depends on the cell, species and conditions in question (Okoli et al. 2021, Yip 2020), with the most recent advancement being nano delivery (Duan et al. 2021). CRISPR has thus far been used in a wide range of areas (Hsu et al. 2014), from medicine and development of therapeutic treatments (Luthra et al. 2021) to plant (Zhu et al. 2020) and animal breeding (Jabbar et al. 2021).

1.2 GMO legislation

GMOs are regulated differently in different countries (Ishii & Araki 2017; Turnbull et al. 2021). One way of separating GMO regulations is based on whether they are triggered by the products or the certain processes creating products. In product-based regulations specific products qualify for assessment according to the national legislation, and in process-based regulations qualify all organisms produced by specific techniques given in the regulation (Ishii & Araki 2017). In the EU and in Norway the technology used qualifies an application for the GMO legislation, therefore we can say the legislations are process-based. It is, however, the product itself which is subsequently assessed (Myskja & Myhr 2020). Further, genome-edited organisms are considered GMOs both in Norway and in the EU, which I elaborate on below (European Court of Justice 2018). This section therefore describes regulation of GMOs, but I will return to the debate on including genome-edited organisms in GMO legislation later in the chapter. Before describing the Norwegian regulation in detail, I briefly describe the EU GMO legislation and the Cartagena Protocol under the Convention of Biological Diversity (CBD). Both of these are external obligations which provide the Norwegian Gene Technology Act with direction and context.

Since 1994, regulations in Norway have been bound to EU legislation through the European Economic Agreement (EEA) (Ministry of Foreign Affairs 2021). The EU has a GMO legislation system containing both guiding directives and mandatory regulations. The *directives* describe goals for member states to achieve, but it is the responsibility of member states to create laws according to these directives. The *regulations* are to ensure common regulation across the EU (EU n.d.). This allows member states to adapt the EU legislation to fit with their individual countries' societal and cultural differences and internal legislations. Here I only emphasize some of the directives. The requirement for case-by-case risk assessment of effects on human health and the environment is established in "Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC". The objective of this directive is to "protect human health and environment" by applying a precautionary approach whenever a member country is placing such products on the marked or for other reasons deliberately releases a GMO. A GMO should not be deliberately released before the national competent authority in a given member state has given their consent based on a risk assessment conducted by the European Food Safety Authority. While the decision on a GMO applies to all member countries, Directive (EU) 2015/412 (amending Directive 2001/18/EC) allows member states to make other considerations in a decision to prohibit a GMO in their territory, such as socio-economic or public policy considerations (EC n.d.).

The CBD is a global forum addressing biodiversity issues. It was first signed in 1992 and entered into force in 1993. This is a global approach to biosafety with regards to GMOs, which in the protocol are called LMOs (living modified organisms). The CBD started working with the transboundary movement of living modified organisms in 1995, which led to the Cartagena Protocol entering into force in 2000. The protocol functions as an international regulatory system, guided by the precautionary principle. In addition to describing a risk assessment, the Cartagena Protocol Article 26 encourages signatories to take specific socio-economic considerations into account. It specifically emphasizes the potential impacts modified organisms may have on local and indigenous peoples (CBD 2000), which often have a deeper connection to biodiversity than society at large (Mazzocchi 2020). Norway became one of 173 signatories in 2000, entering into force in 2003. In paper II we state that China hasn't signed the protocol, however this is not correct as China signed in 2000, entering into force in 2005. (CBD 2022).

1.2.1 The Norwegian Gene Technology Act

The Norwegian Gene Technology Act (GTA) of 1993 (Ministry of Climate and Environment 2005a) regulates the production and use of GMOs. The purpose of the GTA (§1) is:

> […] to ensure that the production and use of GMOs […] take place in an ethically justifiable and socially acceptable manner, in accordance with the principle of sustainable development and without adverse effects on health and the environment.

Cloned animals are also covered by the Act. The GTA was created prior to the EU GMO legislation, but has later been harmonized through the EEA directives regarding environmental protection, contained use of GMOs, and release of GMOs (Ministry of Climate and Environment 2005a,b). In the GTA §4, a GMO is defined as any organism "[…] in which the genetic material has been altered by means of gene or cell technology". Cell technology is not further discussed here. Gene technologies are defined as "techniques that involve the isolation, characterization and modification of heritable material and its introduction into living cells or viruses". A GMO approved for use in the EU is, through the EEA, also approved in Norway. However, Norway, like all EU members, can prohibit the organisms based on to a national impact assessment on a case-by-case basis (Ministry of Climate and Environment 2005a, §10). The requirements to assessment of risk to health and the environment are identical to those in the EU. Further, as cited above, the GTA includes the criteria of sustainability, societal acceptability and ethical justifiability (Ministry of Climate and Environment 2005a, §1). Because these requirements are not directly related to safe use, Zetterberg and Björnberg (2017) have termed them *non-safety* criteria. Several official bodies are involved in assessment of GMOs. The Norwegian Environment Agency (NEA) is the coordinator for the assessment process. The Norwegian Scientific Committee for Food and Environment together with the Norwegian Food Safety Authority assess the organism for risk to human health and environment. The Norwegian Biotechnology Advisory Board (NBAB) is responsible for assessing the non-safety criteria. The NEA recommends a decision to the Ministry of Climate and Environment. Finally, the government makes the decision to approve, limit or prohibit the release of the GMO (Ministry of Climate and Environment 2005a, §10).

While a GMO can only be approved in Norway if there is no risk to human health and the environment, the societal utility and contribution to sustainability must be emphasized in the decision (Ministry of Climate and Environment 2005a, §10). Norway has only approved six GMOs thus far, which are six variants of a GM carnation with changed color (NEA 2021). In total, 12 GMOs have been prohibited on the basis of containing antibiotic resistance genes or posing other risks to health and/or the environment (Lovdata 2017; Myskja & Myhr 2020), while only one GMO has been declined based on the non-safety assessment. This was in 2017 when a GM maize resistant to the herbicide Glufosinate Ammonium was filed for use in Norway. The herbicide was prohibited for use in Norway at the time because of risk to health and the environment. The NEA recommended approval of the crop because the crop itself was not considered a risk to human health and the environment. The government, however, concluded that the crop should be prohibited in Norway because it could not be considered ethically responsible to import a crop designed for use with a herbicide prohibited in Norway due to health risks. In addition, approval was considered not sustainable in a global perspective, and the crop had no societal utility in Norway (Ministry of Climate and Environment 2017).

In 2000, the NBAB produced a guideline for the operationalization of sustainability, societal utility, and ethical justifiability (English version, NBAB 2009) at the request of the Ministry of Climate and Environment. The report listed six topics and respective control questions related to assessment of sustainable development (Table 1) (NBAB 2009). This list is now included in regulation (Ministry of Climate and Environment 2005b).

Table 1 The structure of sustainable development check list in Annex 4 IV of the "Regulation relating to impact assessment pursuant to the GTA" (modified from Ministry of Climate and Environment 2005b).

Topic	Control question
Global impacts	Will there be global impacts on biodiversity? Will there be impacts on ecosystem functioning? Will there be differences between the impacts of production and use in these respects?
Ecological limits	Will there be any impact on • the efficiency of energy use? • the efficiency of other natural resource use? • the proportions of renewable and non-renewable resources used? • emissions of global and transboundary pollutants? Will there be any particular impact on greenhouse gas emissions? Will there be differences between the impacts of production and use in these respects?
Basic human needs	Will there be any impact on the degree to which basic human needs are met? Will there be differences between the impacts of production and use in these respects?
Distribution between generations	Will there be any impact on the distribution of benefits between generations? Will there be any impact on the distribution of burdens between generations? Will there be differences between the impacts of production and use in these respects?
Distribution between rich and poor countries	Will there be any impact on the distribution of benefits between rich and poor countries? Will there be any impact on the distribution of burdens between rich and poor countries? Will there be differences between the impacts of production and use in these respects?
Economic growth	Will there be any impact on the use of energy and other natural resources for economic growth? Will there be any impact on the global/transnational environmental impacts of economic growth? Will the there be any impact on the distribution of economic growth between rich and poor countries? Will there be differences between the impacts of production and use in these respects?

1.2.2 Omitting genome-edited organisms from regulation

The potential use of genome editing technologies in breeding has triggered a debate on how to regulate GMOs. It has been suggested that genome-edited organisms should not be considered GMOs because genome editing allows for making mutations without inserting foreign DNA

(SDN-1). Further it is argued, that lacking such a transgene mutation, these organisms are similar to conventionally bred, or even wild, relatives (Custers et al. 2019; Hallerman et al. 2022). In addition, in comparison to GM techniques, where the placement of DNA is random, genome editing allows for targeted mutation following from the site-specific nuclease cleavage. Altogether, these aspects are used to suggest that genome-edited organisms should not be regulated as GMOs (Ishii & Araki 2017).

In 2018, a case was ruled in the Court of Justice of the European Union deciding that organisms changed using new mutagenesis techniques (this includes genome editing) are to be considered GMOs. The basis of the ruling was that these techniques allow organisms to be changed in ways that do not happen naturally, generating similar effects to transgenesis, including "[…] varieties at a rate out of all proportion to those resulting from the application of conventional methods of mutagenesis" (Court of Justice of the European Union 2018). Omitting genome-edited organisms from the GMO Directive 2001/18/EC on deliberate release of GMOs into the environment was considered to "[…] compromise the objective pursued by that directive, which is to avoid adverse effects on human health and the environment and would fail to respect the precautionary principle which that directive seeks to implement" (Court of Justice of the European Union 2018).

This ruling triggered intense debate. The supporters of omitting genome-edited organisms from GMO legislation argue that such deregulation will democratize the technology. Presumably, it is too difficult to get GMOs approved, which reduces the possibilities of developing countries to take part in the benefits from the new technology (Smyth 2022). On the other side, proponents for keeping current GMO regulation for genome-edited organisms argue that we still lack knowledge about potential unwanted consequences of genome editing, for the environment and the organism itself (Stokstad 2018). Subsequent to this, the EC has continued to investigate the conditions for use of genome editing, and the potential regulatory frames (EC 2021).

The regulation debate has also reached Norway. In 2017, The NBAB proposed a new legal draft for the GTA arguing that the requirement for risk and non-safety assessment should be based on the different levels of genetic interference genome editing allows for: SDN-1, SDN-2 and SDN-3 (see Figure 1) (English version, NBAB 2018b). The proposed model implies that the different levels should be regulated with different requirements for risk assessment and non-safety assessment. The NBAB also held a public hearing on the proposed new model in 2017. This hearing process was later discussed by Kjeldaas et al. (2021), who argue that the broad range of concerns in the hearing answers are not sufficiently included in the NBAB's concluding report (NBAB 2018a). In 2020, the Norwegian Government appointed an expert group, *Genteknologiutvalget,* to assess the new genome editing technologies and advise on whether Norway should rewrite the GTA or not. The expert committee will present their report in 2023 (Genteknologiutvalget, n.d.).

1.3 Atlantic salmon

1.3.1 Aquaculture in Norway

Globally, "blue foods" are being explored, improved, debated, researched, and eaten (BFA 2021), and according to the High-Level Panel for a Sustainable Ocean Economy, foods from the ocean could potentially increase a six-fold (Stuchtey et al. 2020). The Blue Food Assessment Policy Report, an initiative which is the ocean equivalent of the EAT Lancet report, states that to achieve the UN sustainable development goals, the world food systems need to transform, and food from the ocean is an important part of this shift (BFA 2021). The advantage of harvesting and farming foods in the ocean and inland water systems, is that in comparison to terrestrial animal protein, it has higher nutritional content and diversity (Golden et al. 2021), is more climate friendly in terms of environmental footprint (Bianchi et al. 2022), and is already "a cornerstone of many rural and national economies" (BFA 2021, p. 7). In this transformation, Norway is intended to play a leading part.

Presumably, the first time aquaculture was mentioned in Norway was in 1912, when a man got governmental funding to develop production of trout in sea water. He used fish waste to feed the trout, and in the beginning, the trout were thriving. This innovation was described as having a huge potential for the national economy. The man even got an exemption from the Conservation law to harvest fish for spawning. This early trial did not go too well (NENT 1993), but the ocean farming dream was not forgotten. In the 1950s and -60s, various attempts were made to farm fish. From 1971 to 1972, the number of cages in the sea went from 2 to 14, and the production of salmon rose from 100 to 320 tons (NENT 1993). Since then, Norwegian aquaculture has been considered a financial success and today, farming of salmon in Norway is a profitable, technology driven industry on the rise (Afewerki et al. 2022; Hersoug 2015). Norway is the largest producer of salmon on a global scale, with the value of slaughtered salmon being 75 billion NOK (≈ € 7 billion) in 2021 (Directorate of Fisheries 2022c). The industry employs about 9000 people in Norway (Directorate of Fisheries 2022a,e), and is considered important for many rural settlements, especially through family and locally owned companies (Ministry of Trade, Industry and Fisheries 2021). In 2021, 73% of the total number of companies were family-owned, and these controlled 49% of the total production capacity even though they often hold fewer permits and produce less per company compared to non-family-based companies (Nyrud & Mikkelsen 2021). The political ambition is to increase the production of salmon in Norway. For some time, the goal was said to be a five-fold increase by 2050. This ambition was based on a report (Olafsen et al. 2012) that was much criticized (see e.g., Reinertsen & Asdal 2019) and more recently, the political agenda seems to have faded. In the latest governmental aquaculture strategy, the ambition is to "increase aquaculture within sustainable frames" (Ministry of Trade, Industry and Fisheries 2021, p. 8).

Salmon production along the Norwegian coast is divided into 13 production zones, wherein the production is strictly regulated. Any expansion depends on many parameters to be considered, such as coastal zone management, the environment, fish welfare, salmon lice (*Lepeophtheirus salmonis*) infestation rate and wild salmon conservation. Permission to establish and expand aquaculture activity is regulated by the Aquaculture Act (Ministry of Trade, Industry and Fisheries 2005), and the process depends on whether the fish will be grown for food, or other purposes such as research and development, education, exhibition, or for having sea-based brood stock (Directorate of Fisheries, n.d.). Permission to produce fish to be used as food implies permission to produce a specific species in a specific location, within the limit of a given metric ton biomass (MTB) (Directorate of Fisheries n.d.). Briefly, permits are given after consideration of whether this is environmentally responsible, requiring that the farm will not interfere with other regulations, or the use of local area use, biodiversity or cultural monuments (Ministry of Trade, Industry and Fisheries 2005). Recently, the Traffic Light system (reviewed in Hersoug 2021) was introduced to regulate the capacity of salmon farming according to salmon lice infestation mainly because of the negative impact this has on the wild salmon stocks. The presence of a salmon farm production systems in open sea cages increases growth in the salmon lice populations (Dempster et al. 2021), which may have impacts on infection levels in wild Atlantic salmon and sea trout (*Salmo trutta*) (Thorstad & Finstad 2018). The introduction of this system has led to debate because some zones along the coast have been required to reduce production (Osmundsen et al. 2020). Currently, there is also an ongoing debate on taxes, as the government has suggested taxing revenues and investments, to share the benefits of aquaculture with society (Ministry of Finance 2022).

The salmon is an anadromous species, living first in fresh water and later in salt water. Farming it thus requires two phases to mimic this life cycle. The juvenile fish are raised in land-based facilities which simulate the river, before they are put to sea in net pens to grow, and then slaughtered before they mature. By the end of 2021, the standing stock of salmon in grow-out facilities was 426 million individuals (Directorate of Fisheries 2022d). The highest loss of individual salmon is mainly in the freshwater phase, amounting to 134 million individual hatchlings in 2021 (Directorate of Fisheries 2022f). However, considering the amount of effort (in costs and time) during production, the mortality numbers in the grow-out phase, which was 60 million individual salmon in 2021 (Directorate of Fisheries 2022b), are more severe for production, and this thesis will mainly concern fish from that phase.

Young et al. (2019) analyzed and compared ecological and social challenges of aquaculture between "five wealthy nations" and concluded that Norway is mainly challenged by issues which stem from environmental conditions, but which have political effects. One of these challenges was regarding the health of farmed fish (Young et al. 2019). The annual fish health report by the Veterinary Institute in Norway (Sommerset et al. 2022) considers mortality a general indicator of fish health and welfare. Loss of individuals in production is caused by dead fish (81,3%), outtake removed at slaughter (5,9%), escapees (0,1%) and other factors (12,7%, not any of the former) (Directorate of Fisheries 2022b). These numbers cover food fish, brood stock and fish from research and development and education licenses. Even though the numbers vary from year to year, the percentage distribution between the four categories remains mostly the same. Cardiomyopathy syndrome (CMS), injuries after mechanical removal of salmon lice and winter ulcers are among the main reasons for dead fish in food fish production (Sommerset et al. 2022). Details of some of these challenges are elaborated in the discussion.

The Aquaculture Act requires farming to be conducted in an environmentally responsible way (Ministry of Trade, Industry and Fisheries 2005, §10). Still, the other major challenge hindering expansion of Norwegian salmon farming is the impact escaped farmed fish have on wild stocks, through spread of disease and interbreeding (Young et al. 2019). When farmed salmon escapes, they can reproduce with wild salmon which reduces the genetic diversity and viability of wild stocks. Both escaped and reared salmon contribute to potential spread of diseases to wild relatives (Grefsrud et al. 2022; Skaala et al. 2012; Thorstad et al. 2022). The relative percentage of escaped salmon has declined during the last decade. However, the number of escaped salmon in 2021, about 61 000 individuals (Directorate of Fisheries 2022b), is high considering that the wild salmon standing stock is about 300 000 maturing individuals (Thorstad et al. 2022, p. 25).

1.3.2 Domestication of salmon

Once the potential of farming salmon in the ocean was acknowledged, major efforts were made to establish an industry, and the focus was on applied research to propel development (Ministry of Trade and Fisheries 1977). A major contribution to this was, and is, the salmon breeding program. Gjedrem (1985, p. 233) called for the need to develop a breeding program to "[…] make the animals conform to existing environmental conditions." Already in 1976, he stated that it was no longer a question about whether a salmon farming industry would develop or not, but rather a question of its limits to growth. The salmon should be considered a farm animal like any other farm animal, and it was time to develop a breeding program for the species through systematic research on trait selection. The short life cycle interval in salmon compared to terrestrial animals indicated that it would be possible to quickly achieve high genetic gain (Gjedrem 1976). The national breeding program included eggs from over 40 rivers in Norway, to establish a base population. Offspring from different rivers were inbred and cross-bred (Gjedrem 1985) over generations, first based on growth capabilities, followed by other commercial traits to address the efficiency of the industry, but also the challenges it faced over time; age at sexual maturation, resistance to different diseases, quality, growth, and aesthetic characteristics (Thodensen & Gjedrem 2006). Advancing the breeding objectives was enabled by a breeding strategy which uses individuals within and across different families based on the characteristics of "sacrificed" full- and half-siblings. This was a more sophisticated alternative to mass-selection, where individuals are selected based on live-animal measurable traits such as growth (Thodesen & Gjedrem 2006).

Today, selective breeding based on genomic selection allows for more efficient and predictive breeding than the older strategies. In a genomic selection strategy, individuals are selected for breeding based on the genotypic and phenotypic traits of reference organisms and available reference genomes (Houston et al. 2020). Detailed knowledge about the genetic profile of a family leads to more predictive breeding results, which have been accelerated by improvements in sequencing and bioinformatics (Houston et al. 2020; Tsairidou et al. 2020). Selective breeding programs can also use marker-assisted selection (MAS), targeting genetic markers of quantitative trait loci (QTL), which are sequences in the DNA especially affecting the variability of a gene (Meuwissen et al. 2001). This has been especially successful in breeding for resistance to various traits (Kjøglum et al. 2008; reviewed in Song et al. 2022,). For a more extensive review of gene technology tools used in salmon breeding, see Houston and Macqueen (2019).

The breeding in combination with the development of vaccines, has generated a salmon that is protected against several diseases, and at the same time has a high growth rate (reviewed in Thodesen & Gjedrem 2006 and Song et al. 2022). One challenge has been related to create a sterile salmon. One method is to induce triploidy, where fertilized eggs are treated with hydrostatic shock, which increases the number of chromosomes from two to three, rendering the adult salmon sterile (Benfey & Sutterlin 1984). The triploid fish have later showed impaired welfare and have been more vulnerable to the farming conditions (eg. Madaro et al. 2021), which has led to some controversies about generating such fish. Recently, the production of triploid salmon is to be phased out because of fish welfare concerns (Moore 2021).

A recent alternative to the triploid sterile fish, and a potential additional tool in the selective breeding strategy, is to use genome editing, such as CRISPR, to target and change specific traits. However, traits are not always based on one gene, but on several different genes expressed in concert, polyploidy. This makes genome editing challenging, because in such cases it is necessary to identify and target all the relevant sequences (Robinson et al. 2022). Salmon lice resistance is one such trait in Pacific salmon that is polyploid (Kjetså et al. 2020). The breeding of salmon is especially challenged as the salmonids have been through four whole genome duplication events, which implies that genes are present with paralogues that have either the same, a new or no function (Houston et al. 2020). Another challenge is to combine different desired traits and avoid results where one trait, e.g., disease resistance, negatively affects another such as growth (Robinson et al. 2022). Thus far in Norway, sterility (Güralp et al. 2020; Kleppe et al. 2022; Wargelius et al. 2016), lice resistance (Nofima 2021b), CMS resistance (Nofima 2021a), omega-3 production (Datsomor et al. 2019a,b) and pigmentation (Edvardsen et al. 2014) in salmon are the main researched traits using CRISPR. This is further elaborated in paper I.

1.3.3 Wild salmon – a culturally and ecologically significant species

The wild Atlantic salmon is one of three salmonids residing naturally in Norway – together with brown trout and Arctic charr (*Salvelinus alpinus*). The salmon life cycle is, compared to other fish cycles, one of the most studied globally (Birnie-Gauvin et al. 2019). The salmon start as an egg deep in the gravel of the riverbank. Then, it spends its first 3-4 years in the river before smoltifying, which is when the body changes, most importantly the osmoregulation, and prepares for a life in salt water. The smolt migrates into the ocean during early summer and spends at least 1 year pelagic in deep oceans before returning to the river, where it was born, to spawn. Other potential events are autumnal downstream migration of juveniles not adapted for a saltwater environment, iteroparous behavior (repeated spawning) where kelts return to the sea after spawning and repeat the process, and straying – when salmon go up other rivers than their home river to spawn (Birnie-Gauvin et al. 2019). These add complexity to the life cycle, salmon adaption and evolution, and management of the salmon (Birnie-Gauvin et al. 2019). About 20% of the global salmon population is returning to Norwegian rivers (Vollset et al. 2022). Therefore, Norway has a special responsibility for conserving the species under the Convention for the Conservation of Salmon in the North Atlantic Ocean (Eur-Lex 1982), which established the North Atlantic Conservation Organization (NASCO) in 1984 (NASCO n.d.). The Norwegian population is widely spread across 450 rivers along the coast (Hesthagen et al. 2021).

According to the annual report on the state of the wild salmon in Norway (Thorstad et al. 2022, p. 24), the overall number of salmon returning to the rivers has decreased by 50% since the 1980s. In 2021, the wild salmon was rated as a near threatened species and consequently included in the red list of species in Norway. This evaluation is based on the overall decline in mature salmon *returning* from the ocean into the rivers from the 1980s until 2019, with a 21-25% decline in each generation (15-18 years) (Hesthagen et al. 2021). One of the main factors affecting the survival and adaptability of wild salmon stocks are interbreeding with escaped farmed salmon and spread of lice from the farming facilities. The annual report on wild salmon report that a total of 150 populations have been affected by breeding between farmed and wild salmon (Thorstad et al. 2022, p. 10).

The salmon has been an important species in Norwegian culture and economy (Myrvold et al. 2019) since it was established as a species in the Norwegian rivers after the last ice age (Rybråten & Gómez-Baggetun 2016). Myrvold et al. (2019) mapped the cultural, societal and economic value of salmon across the North Atlantic through IPBES' framework of nature's contribution to people, and found that the salmon mainly have cultural and provisional value, as food and an economic income. But in addition to this, salmon across the North Atlantic has non-materially value "[…] through the experiences gained from different forms of fishing, but also to people not fishing, through contributions to their identity, learning and inspiration and future options" (Myrvold et al. 2019, p. 11). Norway is also the country with most salmon fishers, mostly in river fishing, while the number of sea salmon fishers has decreased (Myrvold et al. 2019).

Similarly, the salmon is an important species in the Norwegian indigenous peoples Sámi traditional knowledge, language and culture (see e.g., Joks & Law 2017; Rybråten & Gómez-Baggetun 2016; Sámi Parliament 2021). In paper II and III we present Sámi resource management and citizens together with the other stakeholders and citizens. There is, however, and important difference between these and other participants, as the Sámi hold not only interest in, but also rights regarding, the wild salmon. Therefore, I elaborate shortly here on the importance of salmon to the Sámi peoples. The wild salmon is especially important for river and sea Sámi settlements, and for the preservation, development and transfer of the Sámi culture. While the salmon is not first and foremost important for survival, having it as an available resource for future generations is still one of the main goals for the Sámi Parliament (Sámi Parliament 2021). This is grounded in the word *birget* or *birgejupmi* which means to get by on nature's resources, and to have enough food to survive. It includes an understanding of the need to preserve enough resources for everyone in the Sámi community, and for generations to come (Helander 2004, as translated in Riseth et al. 2010). According to the Sámi Parliament, the "[s]almon farming industry is growing at the expense of the wild salmon as well as the traditional Sámi sea salmon fisheries and other traditional salmon fishing" (Sámi Parliament 2021, p. 14). The Sámi Parliament is therefore calling for more balanced use of the three sustainability pillars, environment, society and economy, and for including traditional and local knowledge in the management of salmon (Sámi Parliament 2021). They argue that local management and management grounded in Sámi values that respect nature, taking all threats into account, not just one at a time, will ensure sustainable use of the salmon resource (Sámi Parliament 2021).

The Sámi traditions, rights and management are included and protected in both international and national legislation. Internationally, indigenous groups are included in the Convention of

Biological Diversity (CBD 2000). Articles 8j and 10c describe how traditional knowledge, ways of living and innovation impacts sustainable resource management, and shall be respected, preserved and continued to the best of the signatory's ability, which includes Norway (CBD 2000). ILO convention number 169 on indigenous and tribal people's rights was ratified by Norway in 1990 and states that all indigenous and tribal peoples shall be allowed to "[…] retain their own customs and institutions […]", and this shall be supported by the authorities (ILO 1989, article 8). The protection of traditional knowledge and management is also described in the UN (2007) Declaration on the Rights of Indigenous Peoples:

> Indigenous peoples have the right to maintain, control, protect and develop their cultural heritage, traditional knowledge and traditional cultural expressions, as well as the manifestations of their sciences, technologies and cultures, including human and genetic resources, seeds, medicines, knowledge of the properties of fauna and flora […]

In Norway, we find protection of Sámi traditional knowledge in the Nature Diversity Act of 2009, where the main objective is to take care of nature for the sake of human utilization of nature as resource(s), recreation and culture, and especially as a foundation for Sámi culture (Ministry of Climate and Environment 2009, section 1). The Sámi Act of 1987 "[…] enable[s] the Sami people in Norway to safeguard and develop their language, culture and way of life" (Ministry of Local Government and Regional Development 2007, §1). Still, the conflict in Norway is characterized by the Norwegian government requiring conservation of nature resources such as salmon rivers based on empirical data and analysis made by natural scientists, while Sámi interests are to conduct sustainable use of the resources in line with the value of *birgejupmi* (Riseth et al. 2010; Sámi Parliament 2021).

1.4 Sustainability

Sustainability is a broad concept with various associations and connotations. In the following I describe some historic roots of the concept, current understandings, and theory on how to operationalize it in assessments.

1.4.1 From concept to operationalization

Du Pisani (2006) has published a review of the history of the term and concept sustainable development, with an emphasis on how different words have been used for this concept. The word "sustainable" has a more recent origin, but older words show traces of the same mindset regarding the development of human life and utilization of natural resources. In order to keep the historical review brief, I limit the concept of development to acknowledging that different cultures and religions have different perceptions about whether time is linear or not (Du Pisani 2006).

At several times throughout history, the human-nature relationship and the use of resources have been described through terms like *nachhaltende Nutzung* (sustainable use) and der *ewige Wald* (the eternal forest), which resemble the wider concept of sustainable development we use today. Several people have at different points addressed issues related to a growing population and exploitation of resources (Du Pisani 2006). During the 20th century, the realization of human impact on nature caused by the growth in population, production and consumption, and the ensuing consequences, was described and discussed by people like Rachel Carson in *Silent Spring* (1962), which really sparked a fire in the environmental debate. A decade later, the report *Limits to Growth* (Meadows et al. 1972) was published. The main conclusions were that there are thresholds, or limits, to growth, in the population, exploitation of natural resources and food production, which humans will reach faster if the growth is not slowed down. In addition, it was pointed out that the consequences of reaching the thresholds are unknown, but probably unwanted. Reaching some kind of equilibrium should be possible, in terms of equality between people and equilibrium in ecological-economic activities, and the report called for efforts to start investigating how to reach that equilibrium (Meadows et al. 1972).

Another decade later, in 1983, the Secretary-General of the United Nations asked the Norwegian politician, Gro Harlem Brundtland, to gather a commission on "a global agenda for change" (Brundtland et al. 1987, Chairman's foreword). This commission was to set a long-term strategy for the strengthening and conservation of the environment, including global cooperation on environmental issues, with emphasis on the relationships between population, resources, environment, and development. The result was the report *Our common future,* in which sustainable development was defined as "development which meets the needs of the present, without compromising the ability of future generations to meet their own needs" (Brundtland et al. 1987, chapter I). In addition to this definition, the focus throughout the report was on the dimensions *environment*, *society* and *economy*, and the relationships between these three spheres. These have also been termed the three pillars of sustainability, and the approach is (often in politics and economics) to balance the pillars (Elkington 1998, reviewed in Alexander et al. 2020) or focus on one of them.

Global cooperation was also on the agenda in 1992, when the UN Conference on Environment and Development was held in Rio de Janeiro, which led to the establishment of *Agenda 21*. The report from this conference stated that the world is facing challenges which are beyond saving country by country. Instead, countries must come together under common goals for change, to ensure "[…] fulfilment of basic needs, improved living standards for all, better protected and managed ecosystems and a safer, more prosperous future" (UN 1992, chapter 1). *Agenda 21* was followed up by the 5 Millennium Goals in 2000, which were set to be achieved by 2015. In 2015, the UN redefined the goals in *Agenda 2030* in the sustainable development goals (SDGs) (UN 2015). These are based on the thoughts of Brundtland et al. (1987) and are 17 people-centered goals with 169 targets in total, focusing on eradicating poverty – the greatest global challenge. The SDGs are integrated in each other, emphasizing that "everything depends on everything", and balance the three dimensions of sustainable development, environment, society and economy (UN 2015).

The SDGs have been criticized for being hard to measure, too ambitious, complicated, non-binding, and for giving top priority to everything, leaving nothing to be of main priority in the attempt to make the goals as general as possible (Swain 2017; van Vuuren et al. 2022). Some targets are also contradictory, and terms such as animal welfare are not even mentioned (Torpman & Röcklinsberg 2021). With regards to the operationalization of the goals, the structure of a list is open to cherry-picking, as they do not present what is at stake if an organization, industry or country attempt to prioritize certain goals over others. On the other hand, an advantage of the SDGs is that they provide us with common goals to discuss, implement and improve. An example of how this can be utilized in practice is how Norwegian strategies such as the governmental aquaculture strategy have implemented the goals (Ministry of Trade, Industry and Fisheries 2021).

1.4.2 A biosphere-based sustainability perspective and the planetary boundaries

As mentioned above, one common approach to sustainability is attempting to balance the three pillars environment, society and economy. Alternatively, one can choose to prioritize one of them, usually environmental sustainability. In this section, I briefly describe a direction of sustainability science that has gone beyond this approach. In biosphere-based sustainability science, society and economy are acknowledged to be subsystems of the environment – the biosphere (Folke 1991; Folke et al. 2016). From this perspective, it is not sufficient to prioritize either one pillar or the other, because they are intertwined in larger systems with nature as the foundation (Clark 1986; Folke et al. 2016). Furthermore, the biosphere is not infinite in its provision of ecosystem services and resources (Brauman et al. 2019). This is already evident, e.g., in the declining biodiversity and changing climate (Pörtner et al. 2021). Accordingly, there are some limits to human development.

Finding the limits to human activity on, and exploitation of, the Earth have been presented in a framework for tracking the human impact on Earth systems – *the planetary boundaries* (Rockström et al. 2009). In this publication, the authors emphasize that we have left the era named the Holocene, where Earth systems remained fairly stable and could have continued to do so if not for the activities initiated at the rise of the Industrial Revolution in the mid-19th century. Industrial production and consumption, pollution, deforestation and so on have led to a less steady state – the *Anthropocene*, the age of humans. The authors argue that it is time to steer the environmental conditions back to how things were during the Holocene, and present nine boundaries within which human activities can go on without straining the state of the Earth systems – a safe operating space (Rockström et al. 2009). The research conducted thus far has attempted to determine the thresholds to which a given system could "[…] shift into a new state, often with deleterious or potentially even disastrous consequences for humans" (Rockström et al. 2009, p. 472). According to the most recent updated analysis, we have now crossed the threshold of safe operating space for five of the nine planetary boundaries: Biosphere integrity/genetic diversity, land-systems change, biochemical flows, climate change (Steffen et al. 2015), and novel entities (Persson et al. 2022). The latter have only yet been quantified for plastic and chemical pollution, while novel organisms (such as GMOs) have not (Steffen et al. 2015).

The term Anthropocene was introduced by Crutzen and Stoermer in a newsletter to the International Geosphere-Biosphere Programme in 2000. They suggested that due to the changes that humanity is causing to the environment and the Earth, the geological epoch should be termed the Anthropocene (Crutzen & Stoermer 2000). It has since been widely adopted, perhaps especially in research concerning Earth systems and planetary boundaries. However, there are different opinions on the term Anthropocene (Emmett & Nye 2017, p. 98). Donna Haraway (2015) stated in a comment to the Environmental Humanities journal that even though anthropogenic processes can be acknowledged, it is not so much that people live on Earth that is the problem, it is what we do, and other terms might therefore be more appropriate, such as

Capitalocene, Plantationocene or Chthulucene (Haraway 2015). I will not go further into this discussion, but it is worth mentioning that the concept in itself is debated, and that a specific definition of the Anthropocene grounded in the natural sciences is also currently under investigation (Gibbard et al. 2022; Steffen et al. 2016).

When integrating sustainability, there is need for an operationalization plan. In 2018, the planetary boundaries were connected to the SDGs in a report to the Club of Rome at their 50 years anniversary (Randers et al. 2018). The report analyzed four plausible scenarios for how the SGDs could be used and sustainable activities conducted: in the same, a harder, a faster or a smarter manner. The latter appeared as the most efficient strategy, requiring policy which encourages transformation, and that development happens within the safe operating space of the Earth systems, where the biosphere is prioritized, as the foundation of human survival (Randers et al. 2018). Approaching the SDGs, systemic changes outside the habitual way of solving issues are needed – not trying faster or harder, but *smarter* (Randers et al. 2018). Other approaches have been to define new quantifiable sustainability indicators within the SDGs (van Vuuren et al. 2022). In this thesis I have used a model combining the biosphere-based sustainability and the SDGs. This is further described in methods section 0.

1.5 Social acceptance

When applying gene technology in food production, it is essential to know how such products are perceived and will be welcomed by the public (Lassen & Jamieson 2006; Myskja & Myhr 2020). In this final section of the introduction, I describe some trends in, and some factors determining, attitudes to GMOs in food production, to give an introduction to social acceptance of GMOs.

1.5.1 Trends in attitudes to GMOs in Europe and Norway

The most consistent and systematic monitoring of people's attitudes to biotechnologies in Europe is the European Commission Eurobarometer (EB). In parallel to several EB surveys, Norwegian public attitudes to GMOs have been studied too (Hviid Nielsen 2007a). The different surveys use gene technology and genetic engineering interchangeably, and I therefore describe their results with respective terms. Mainly, gene technology/genetic engineering was separated from biotechnology (medical applications). Both in Norway and in the EU, the expectations of modern biotechnology increased from 1978 onwards to the beginning of the

1990s, then it had a decline towards 1999. This decline was presumably due to the fact that biotechnology was no longer just something that existed in laboratories, now people had to relate to it, such as gene therapy (reviewed in Hviid Nielsen 2007a). The EB compared perception of gene technology to other technologies such as telecommunication, solar energy and information technology. Early in the 1990s, respondents to the survey (excluding Norway) had the lowest expectations of gene technology. People also had more optimism biotechnology, varying between countries. Regarding "anticipated effects" of technology, some even answered that genetic engineering "would make things worse" (INRA 1993, p. 8). In the late 1990s, support for GM crops and foods specifically declined and genetic engineering had the highest rate of people being unsure about the potential of the technology (EC 1997). In 2002 it was found that "[a] majority of Europeans do not support GM foods", even though this attitude differed across countries and to some extent also sociodemographic background (Gaskell et al. 2003, p. 1).

In 2010, optimism towards genetic engineering and biotechnology increased to 53%, potentially explained by biotechnology and genetic engineering now being joined in one category (TNS Opinion and Social 2010). In this EB, Norway was also included, and data shows Norway to be one of the more positive countries towards genetic engineering. Norway was even the country where most people had heard about GMO foods, despite not having such products available on the marked. More generally, this EB showed suspicion towards GM foods, and people were worried about risks to the environment and human health, and the naturalness of GMOs were questioned. People also though the potential benefit of the products were not fairly distributed in society (TNS Opinion and Social 2010).

More recently, surveys of Norwegian citizens' attitudes towards GM and genome-edited foods have been published (Bugge & Rosenberg 2017; Bugge 2020; NBAB 2020). Three important disclaimers are i) none of the reports are peer-reviewed, ii) the reports describe the technology using different terms, and iii) while investigating the same topics, dissimilar conclusions are drawn. The two latter issues have been commented in the media as problematic science communication (Antonsen et al. 2020a,b).

Bugge and Rosenborg (2017) and Bugge (2020) found that 79 and 80% of the participants (N=1041, 1066) had heard about GMOs, respectively. In both these surveys, very few described their knowledge about GMOs as "very good". Most described it as "neither good nor bad". Similarly, the NBAB (2020) asked the participants (N=2016) to rate how familiar they are with "genome modified foods" and "genome editing (often called CRISPR)". These results showed that people had heard about (43%), were a little familiar with (47%), or had never heard about (5%) genome modified foods. Further, the NBAB showed that almost half of the respondents had never heard about genome editing or CRISPR (46%). This indicates that when talking to people about GM foods, choice of terms is important. Further, Bugge and Rosenborg (2017) and Bugge (2020) found that when questioning whether GMOs would be important to agriculture, answers were divided equally between yes, no and don't know. The NBAB found, when asking about the potential of specific applications, that more than 50% of the participants where either a bit or very positive towards applications described to be improving environmental impact and animal welfare. People were, on the other hand, opposed to using genome editing to change esthetic traits or increase production efficiency. All surveys found that most participants questioned the safety of GMOs and/or genome-edited organisms with regard to negative impact on the environment, and human and animal health. Both surveys also attempted to ascribe the degree of acceptance to GMOs or genome-edited organisms to the level of knowledge among the public. However, as already pointed out in both Antonsen et al. (2020a,b), measuring the participants' level of knowledge concerning GM foods failed in both surveys as they mix the terms "familiarity with" and "knowledge about". This can be associated with the perspective that the main reason for people's lack of acceptance or support for some new technology or method is insufficient knowledge – the knowledge deficiency theory. This theory has, however, been contested, e.g., by Siipi and Atheensuu (2011) who argue that this model undermines the role of other concerns, such as moral values, in people's decisions.

1.5.2 Factors determining the attitudes to GMOs

Where surveys fall short in terms of determining what is behind the attitudes identified – such as moral values, qualitative methods such as interviews, focus groups and discourse analysis allow for going deeper into the arguments. Here I briefly present some of the important factors determining social acceptance of genome modified and edited organisms. Most of the following studies mentioned are qualitative, but some are reviews of quantitative and qualitative studies. Generally, the social acceptance of GMOs concerns perceived benefits or usefulness, risks, moral concerns about gene technology, potential socio-economic effects, the consumer, and often the question of naturalness is raised (Lassen et al. 2002; Magnus et al.

2009). In addition to this, there are differences in the attitudes regarding GM plants and animals, where people might be more reluctant to accept modification of animals (Marques et al. 2014).

The question of risk is widely discussed with regard to GMOs. Foods carrying negative associations, such as having negative impacts on the environment, human and/or animal health, are less likely to be accepted by the public and are thus less viable as products on the market (Frewer et al. 2004). Public opinion on GMOs depends not only on the risk of harm to human health, but also on broader risks, and perceived risks, needs and benefits of such foods (Frewer et al. 2004). The perception of risk might also vary between different societal groups, because risk perception is influenced by social norms, and in relation to benefit and control (Feindt & Poortvilet 2020). In relation to risk, the familiarity of a product (Robbins et al. 2021) and history of safe use (Yang & Hobbs 2020) are also important for acceptance, across societal groups. It has been suggested that the introduction of genome editing and CRISPR will change people's perception of gene technologies in food production, as several argue that the risk is lower (Gao et al. 2018) and products are more similar to "conventional" products (Abdallah et al. 2015; Singh & Bokolia 2021). Following from this, a challenge often put forward as the currently most important to overcome is the alleged lack of knowledge amongst the public (Hallerman & Grabau 2016).

The perceived utility, such as improved health and environmental conditions, has been a criterion of great importance in the social acceptance of GMOs in Norway (Magnus et al. 2009). When GMOs in foods have not shown substantial benefits to either health or the environment, people do not consider it a "necessary risk" to take (Magnus et al. 2009). Magnus et al. (2009) call it a "wait-and-see" attitude, but it is also similar to applying the precautionary principle (see e.g. Anyshchenko 2019). As with risk perception, previous experience, or lack thereof, with such organisms or foods affects the perception of whether the product is needed or not (Magnus et al. 2009). Lassen et al. (2002) emphasize that the benefit of a GMO can be related to economic benefit to the food producer (the industry), to consumers, or to society. An argument based on utility was used at a Norwegian citizens conference arranged by the National Research Ethics Committees in 1996 to separate animals from plants in the GMO debate. The use of GM on animals was not considered useful enough at the time, and therefore barely discussed (NREC 1996). Such a perspective seems to prevail in the discussion on genome-edited animals. Yunes et al. (2021) conducted interviews and a survey in Brazil on citizens' acceptance of genome-edited cattle. They found that if the technology was implemented to increase growth, or solely for the economic benefit of the industry, acceptance declined (Yunes et al. 2021).

In addition to the questions on risk and utility, several other concerns regarding moral values and socio-economic conditions affect people's perception. Lassen et al. (2002) suggests that perhaps previous conflict about GMOs in the 1980-90s did not concern the safety of GMOs per se, but was a result of "an inability, within science, industry and the public authorities, to understand and/or accept public concerns about GM foods", because the question of social acceptance goes beyond the question of risk (Lassen et al. 2002, p. 264). Frewer et al. (2004) suggest that socio-political attitudes towards e.g., technology and the environment could influence people's attitudes towards GMOs. Historically, GMO crops have been produced and exported by large, multinational companies which society has little influence on and varying benefit from (Lassen et al. 2002).

Amongst ethical and moral issues related to GMOs and genome-edited organisms, the naturalness argument is often used to describe people's perception of GMOs (Bartkowski et al. 2018; van Haperen et al. 2012). This was considered to be hampering the introduction of GMOs to such an extent that the scientific communication of CRISPR intentionally focused on describing the technology as more natural than GM (Doxzen & Henderson 2020). However, the weight of the naturalness argument has been questioned. Perceived naturalness of a GMO will allegedly not determine its overall support in society (Frewer et al. 2011), and naturalness has been suggested to be just as relevant to other agricultural innovations, such as pesticides (Marris 2001). Similarly, Yunes et al. (2021) found that people did not consider genome editing of cattle to be natural, because of the speed of change and the degree of human involvement in the process. The same notion of GM of animals as a "violation of nature" and the speeding up of genetic selection as worrying in itself, was identified in a focus group study two decades ago (Macnaghten 2004).

Labelling GMO products allows consumers to choose whether to eat GMO foods or not, and it has therefore been an important aspect of social acceptance discussions (Lassen et al. 2002; Nauheim 2010). Qin and Brown (2006) explored labelling of GM salmon in a focus group study. They found that some people felt it was necessary to label the salmon, while others did not, because they did not consider the GM salmon to be different from conventionally bred salmon. Ishii and Araki (2016) suggest that labelling could be an important contribution to the introduction of transgene-free genome-edited plant crops, in addition to transparency and public communication.

The arguments and opinions identified in literature and presented above concern both the use of gene technologies and the products they create. In 2007, Hviid Nielsen reviewed the present Eurobarometer data from Norway and argued that it is not the technology itself, but the way it is used which is determining for acceptance (Hviid Nielsen 2007b). Still, studies such as Yunes et al. (2021) show that the process of genome editing cannot be written off as irrelevant to the resulting product, and therefore might impact people's opinions too.

2 Methods

Three methods have been used in the studies underlying this thesis: systematic literature review, document analysis, and interviews. The interviews, as a method, have been used for qualitative sampling and analysis of empirical data. In this section the theory behind, and methodological decisions are described. Some of these descriptions might overlap with what is already presented in papers I-III. The methods chapter is arranged chronologically according to when the activities were conducted. It therefore starts with the literature search, and proceeds with document analysis, followed by sampling and analysis of interview data, before presentation of the methodology used for the sustainability assessment. Larger parts of section 3.2 and 3.3 were developed as an exam essay in KULT-8861 at NTNU.

2.1 Literature search: the PRISMA method

For paper I, we wanted to identify the status of the field of *genome editing in aquacultured fish,* and therefore decided to write a systematic literature review where we identified and described what has been done thus far and what can be considered potential future applications of genome editing in aquaculture. Similar studies had been published ahead of this publication, but to our knowledge, none of these were conducted in a systematic manner. The Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA) (Moher et al. 2009; Page et al. 2021) was chosen as the method for designing the search, and for reporting the results. This is a method for retrieving and systemizing data which allows for mapping the route of the process of systematic data retrieval, and the choices made underway which affect the resulting records (inclusion and exclusion). As seen in other systematic studies (e.g., de Graeff et al. 2019), we based the searches on PRISMA elements of relevance to our study. A detailed description of the systematic review approach is given in paper I. Figure 2 shows a flow chart of the process, based on Table A1 in Appendix 1 of paper I. Table 2 lists the search strings and exclusion lists used. The status of the research field was mapped by arranging the empirical studies according to categories: species, field of interest (aquaculture, teleost genetics, or CRISPR as a tool), type of trait(s) and targeted gene(s), genome editing system, and the institutional affiliation of the first author. A new search (not included in Figure 2) using the complex search string and time frame 2021-2022 in Scopus (Web of Science not available at NORCE) was performed in August 2022 to update the review. The search retrieved 47 records, assessed based on title, of which 26 were included (based on exclusion criteria list C and A), or as duplicates to records in paper I. Results are presented in the discussion.

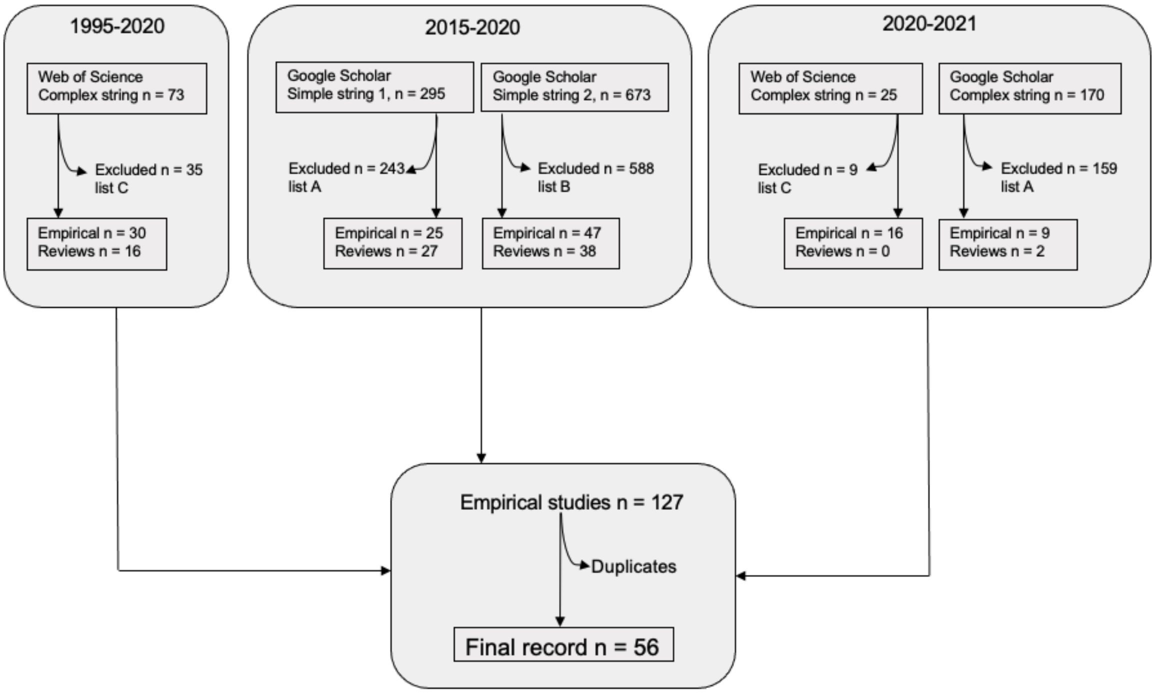

Figure 2 Flow chart outlining the process of systematic literature review conducted and published in paper I. Systematic literature searches were performed limited to three different periods (1995-2020, 2015-2020, 2020-2021), using two different search engines (Web of Science and Google Scholar), three different search strings (Table 2). The searches were performed with two rounds of exclusion, first according to exclusion criteria given in Table 2 and then by removing duplicates. The scheme is based on Table A1 in Appendix 1 in paper I (Blix et al. 2021).

Table 2 Search strings and exclusion criteria used in the systematic review of paper I (Blix et al. 2021).

Search strings	**Simple 1**	crispr/cas9 farmed atlantic salmon
	Simple 2	salmon aquaculture crispr
	Complex	“TALEN” OR ”zinc finger nuclease” OR ”CRISPR” OR ”CRISPR/ Cas9” AND “Grass carp” OR ”silver carp” OR ”common carp” OR ”nile tilapia” OR ”bighead carp” OR ”carassius” OR ”catla” OR ”Osteichthyes” OR ”atlantic salmon” OR ”roho labeo” OR ”pangasius” OR ”milkfish” OR ”tilapia” OR ”clarias” OR ”Wuchang bream” OR ”rainbow trout” OR ”cyprinidae” OR ”black carp” OR ”snakehead” OR ”ctenopharyngodon idellus” OR ”hypophtalmichthys molitrix” OR ”cyprinus carpio” OR ”Oreochromis niloticus” OR ”hypophthalmichthys nobilis” OR ”catla calta” OR ”salmo salar” OR ”labeo rohita” OR ”chanos chanos” OR ”Megalobrama amblycephala” OR ”Oncorhynchus mykiss” OR ”mylopharyngodon piceus” OR ”channa argus”

	A	**B**	**C**
Exclusion criteria	News articles Ethics-related studies Conventional breeding Agricultural species PhD and Master theses Basic research fish health GE feed Patents	Crustaceans miRNA Interference RNA Sex determination Embryonal development	Research in human physiology Microbiology Environmental DNA zebrafish Medaka Virology

2.2 Document analysis

Document analysis is used to study the role of documents and their content. The process of document analysis includes identifying, selecting, evaluating and making sense of information written in, or describing the context of, the documents. Examples of documents are books and newspapers, radio and television program scripts, organizational or institutional reports and meetings reports (Bowen 2009). In paper II we analyzed documents for three purposes (Bowen 2009); i) setting the stage for Norwegian aquaculture, ii) identifying relevant stakeholders and iii) identifying current discussions and challenges, and future prospects and strategies regarding both sustainability in general and sustainability in aquaculture. The data from the documents supplemented other research data, as has been described by Bowen (2009). Documents were identified in an unsystematic manner in the beginning of, and updated during, the project. Identification of relevant documents was done by searching for grey literature, snowball reading using reference lists, at conferences and through media.

For paper II, a list of ten written strategy or policy documents identified were grouped according to whether the global, European, or national level was targeted in the document, and whether it was regarding sustainability in general or sustainability in aquaculture in particular. The documents invite the receivers of the documents, here mostly policy makers, national authorities or citizens, but also private companies, to align their strategies and activities to the directions of the document. In addition to describing how the issue in question looks, and how one can hope to solve it, documents can also affect how an issue is understood and thus evolves (Asdal 2015). All documents used for paper II hold leading positions and are likely to influence further strategies and debates on how to develop food production in more sustainable manners. In paper II, we also listed which other documents each document mentions as either directing or influencing the content of the document. This list shows how all documents selected for the paper are involved with other similar and/or leading documents regarding the issue. E.g., most documents mention the sustainable development goals (UN 2015), which tells us that the documents, at least to some degree, share a common starting position on sustainability.

In addition to analyzing the issuer, context, and related documents, we performed content analysis, assessing the content of the text for how sustainability should be, can be and is understood, and how it is suggested to be operationalized. The data generated from this analysis was used to inform the making of the sustainability assessment framework, merged with the data generated from the analysis of interviews. As the role of the documents was to supplement the interview data by anchoring the framework in current sustainability strategies, the analysis should be considered a surface interpretation of the content (Ryhaug 2002).

2.3 Stakeholder and focus group interviews

The empirical data sampling in the project was done through qualitative stakeholder interviews and focus group interviews. This was to a great extent planned, conducted, and analyzed in cooperation with Hannah Winther. The study design of the project followed six of Kvale and Brinkmann's (2014, p. 128-129) seven stages of an interview inquiry – *thematizing*, *designing*, *interviewing*, *transcribing*, *analyzing* and *reporting*. The *verifying* step has not been given as much attention as the other steps, and a *recruitment* step has been added as this is not included (Kristensen & Ravn 2015) in the list by Brinkmann and Kvale (2014). While the actual process was not linear, this linear process design was useful as a guiding concept, and I will follow it in this section as well, but comment in places where we had to re-assess or reconsider our methodological choices. Being mindful about to what extent we were flexible with the approach was important to us in the learning process. Before describing the overarching approach in the qualitative data sampling and analysis, I will describe some theory of interview as a method, which I have considered during this study.

2.3.1 Interview as method

Conducting interviews – talking to people, is a way for researchers to learn "how people understand their world and their lives" (Brinkmann & Kvale 2014, p. 1). The research interview is a conversation between a researcher, the interviewer, and a person that holds certain experiences or knowledge about the topic that the researcher is interested in (Gubrium & Holstein 2011, chapter 1). The interview itself is an activity where the interviewer and interviewee share their view on the topic, and knowledge is generated in the meeting (Brinkmann & Kvale 2014, p. 3-5; Gubrium & Holstein 2011, chapter 1). The role of the interviewer (which can also be the researcher) in the conversation depend on the approach chosen and how the interview guide is built, this is further described below.

Ryen (2002) states that the qualitative interview is the most common way for the qualitative researcher to gather data (Ryen 2002, p. 10). While quantitative methods aim to declare general observations and "to clearly isolate causes from the effects", qualitative methods, are used whenever there is need to define "subject- and situation-related statements, which are empirically well founded" (Flick 2009, p. 12-14). Both types of empirical data on social acceptance of GMOs are useful. However, Frewer et al. (2004, p. 1187) emphasize in a review that "[q]ualitative investigations provide a much richer understanding of people's concerns and perceptions than surveys." Further, where surveys allow for "quantification of public attitudes", other methods allows for "explain[ing] the content of public concerns" (Lassen et al. 2002, p. 264). The method chosen for identifying conditions for genome-edited salmon to be sustainable and socially acceptable, was qualitative, semi-structured individual stakeholder interviews and citizen focus groups, building on the literature review and document analysis described above.

There is a vast selection of types of interviews (Brinkmann & Kvale 2014; Gubrium & Holstein 2011, chapter 2; Ryen 2002, p. 15,), often related to what the aim of the study is and the degree of structure. *Individual expert interviews* are conducted when it is mainly the person's knowledge about a topic which is of the interest to the researcher, rather than the person overall. In paper II and III we use the term stakeholder interview, but we might as well have called it expert interview because different stakeholders were interviewed on the basis of their knowledge about and role in salmon-related activities. Expert interviews can be used as an "easy" way of exploring a topic, or if the person holds a leading position in their field or organization, this is a way for the researcher to access that organization through this one person (Bogner et al. 2009; Meuser & Nagel 2009). The person can therefore also be seen as representing not only personal interest, but the field/organization in which they are considered an expert (Flick 2009). Here, the interviews thereby contributed as not only discussion on the topics, but as an elongation of the background inquiries about the topics.

In addition to performing individual interviews, we conducted *focus group* interviews. In these, informants are put together in a group, and the data collection is based on the "[…] group interaction on a topic determined by the researcher" (Morgan 1996, p. 129-130). The focus group is different from the individual interview as it offers a "[…] greater breadth" (Morgan 1996, p. 134). Following individual interviews, focus groups can be used to widen the population selection and test the concepts that have been identified in the interviews. In this study, the interviews and focus groups supplement each other as focus groups can be used in an explorative manner, and present the researcher with several different voices and opinions within the group (Morgan & Krueger 1993).

The persons being interviewed can be described as "vessels of information", and the interview is about retrieving that information. How the information is stored, how the interviewer approaches retrieving the information and the mode of the interview situation affect what kind of knowledge is generated in the interview meeting (Gubrium & Holstein 2011, chapter 2). The person being interviewed in a research context has been designated with different terms, and the terms reflect the role of the interviewed person and the relationship between the person being interviewed and the researcher (Gubrium & Holstein 2011, chapter 2). Ryen (2002, p. 17) discusses these terms: *informant* referring to the person as giving information about her/his culture*, respondent/interviewee* implying the person has a passive role answering questions*, co-researcher* referring to the person as having the role as the researcher's co-worker*,* and *member* which implies that the person generates knowledge together with the interviewer. A fourth definition is *participant*, which refers to the person being interviewed as participating in the conversation and the knowledge production (Brinkmann 2007). This is the choice of term for this thesis, considering how the participants contribute through participation in the conversation, with their knowledge and insights. For the "group leader" I use *moderator*, referring to the researcher/interviewer as someone not leading the discussion but guiding and observing it (Mishra 2016).

2.3.2 Thematizing and design

The aim of the study and research questions was elaborated into two *thematizing* texts (Brinkmann & Kvale 2014, p. 128) by Winther and myself, which included the topics moral responsibility for salmon, genome editing, and sustainability, all within the context of Norwegian salmon farming. These texts were then further elaborated in a qualitative operationalization table used to systemize the themes, dimensions, topics and questions for the final interview guide (Appendix 2). The content and structure of the guide were elaborated until agreement in the research group was reached. It was decided that a semi-structured interview guide would be useful for allowing flexibility in the conversations (Flick 2009), and it was arranged according to three themes: *moral responsibility/the salmon*, *genome editing* and *sustainability*. In this way, it was possible to ask different questions within a theme, but still follow a structure in the conversation through the three themes. The guide also included an introduction to the topic and to the CRISPRsalmon project, as elaborated below. When writing the questions, we considered that asking a stakeholder or a citizen "what values are at stake if we genome edit the salmon?" is quite formal and potentially hard to answer. We therefore formulated *introductory* questions which we presumed would generate answers which could be considered values at stake. For example, the question “what do you think about genome editing of salmon?” Or *direct* questions such as “how do we know if the salmon is faring well or not?”. The structure of the interview guide also allowed for asking *follow-up* or *probing* questions by inviting the participant to elaborate on something they just stated, or interpreting questions whenever there was need to clarify a statement (Brinkmann & Kvale 2014, p. 160-162).

After developing the interview guide, and before recruiting participants, the project was approved by the Norwegian Centre for Research Data (NSD) for the sampling and use of personal information. The NSD follows requirements for safe use of research data and sensitive information from the Research Council of Norway, the EU and Science Europe (https://www.nsd.no/en/create-a-data-management-plan). The assessment of processing of personal data can be found in Appendix 3.

2.3.3 Recruiting participants

The literature search and document analysis were used to identifying relevant stakeholder groups and interested parties, and for the thematizing stage of the empirical data sampling. The recruitment process is about deciding who will be most suitable to answer the research questions (Kristensen & Ravn 2015). The main stakeholder groups identified were the farming industry, research and advisory bodies related to farming of salmon and/or gene technology in fish, and groups related to wild salmon management and natural resource use/food production, both advisory and NGOs, and citizens and/or consumers, and these were recruited by Winther and myself. Participants for the focus group interviews with citizens were recruited by IPSOS AS. Recruitment details are given in paper II and III, and invitation letter submitted to stakeholders is attached as Appendix 4. Table 3 shows the distribution of stakeholder groups and focus groups interviewed, based on a table in paper II (Blix & Myhr 2023), and has also been included in paper III. All stakeholder participants had to sign a declaration of consent as part of the NSD data requirements for data sampling through qualitative interviews. Focus group participants consent were arranged by IPSOS.

Table 3 Interview groups with number of interviews per group, modified from Blix and Myhr (2023).

Groups	Number of interviews* (focus groups number of participants x interviews)
Scientists using genome editing in fish	4
Trade union participants	2
Salmon farmers	4
Fish health workers	3
NGO participants	2
Advisory body participant	1
Sami resource management	1
Wild salmon management	2
Focus group Norwegian	6 x 3
Focus group Sámi Norwegian	6 x 1

*The number of participants per stakeholder group varies because groups which work directly with salmon on a daily basis and groups whose information could not be read in a report or in the literature were prioritized.

2.3.4 Conducting interviews

All interviews, individual and focus groups, were conducted by Winther and myself over video calls with the participants, using either Zoom or Teams software. The digital solution was due to the COVID-19 pandemic and limited possibilities for travelling and physical meetings. Individual interviews were conducted between September 2020 and March 2021. Focus group interviews were conducted during April 2021. The same interview guide (Appendix 2) was used both for individual and focus group interviews. The guide included a short opening introduction where we introduced ourselves with name and affiliations, followed by presentation of the topics, including a brief, simple description of what genome editing is and some examples of how it has been used thus far on farmed fish and salmon as reviewed in paper I. We also explained what the aim of the project was, how the data was going to be used in scientific publications, that we wanted to focus on each of the three topics through the conversation, following a three-split structure, and that it would be audio recorded as already declared in the info letter. In the Sámi focus group, we also told the participants that they were all recruited based on their Sámi background. This was not information that IPSOS had given the participants, and we considered it polite to inform them about this. Most of them had already understood this based on the names (which are visible in the software systems). The facilitation of the interviews was split between Winther and myself. Winther asked questions related to topic one which was salmon and human-salmon relations, while I asked questions related to genome editing and sustainability, because this fitted well with the topics of our respective doctoral projects. The two latter topics included short introductions about what genome editing has been used for thus far on salmon in Norway. The introduction to sustainability included brief description about sustainability is linked to aquaculture because it is required that the salmon farming becomes more sustainable, and genome editing because this is a requirement in the Gene Technology Act.

During the course of the project, we made some adjustments in the interview guide. We found some participants were reluctant to answer some of our questions or doubted their own answers because they did not have enough knowledge about genome editing and the ethical issues related to the technology. We therefore also included a declaration that all answers were welcome. Initially, the introduction to sustainability also included the well-known definition from *Our common future* (Brundtland et al. 1987), and I declared that this is one way of understanding sustainability. However, since we found during the first stakeholder interviews that this hindered participants from presenting their own perception of the concept, it was removed from the introduction.

The *stakeholder interviews* were conducted for between 49 minutes and 1 hour and 10 minutes. One interview lasted 1 hour and 34 minutes. After the introduction, we asked the participants to talk about themselves and their occupation and relation to salmon. First, we interviewed the researchers working with farmed salmon and/or genome editing in salmon, as their expert view on the technology could help to broaden our view (Bogner et al. 2009). Despite following the three-split structure of the interview, we allowed the participants statements to steer the pace and order of the questions, in order not to intrude on their line of thought. We also had the participants elaborate on their answers by asking follow-up questions. This was where the semi-structured guide became useful, allowing us to pick the most relevant questions in each conversation. Considering how the interviews were conducted in online video calls, it was difficult to interrupt the participants with structuring questions, whenever the answers were too extensive. As two researchers conducted the interview together each time, we communicated in parallel to the conversation in a private chat room, to ask each other which question to choose next, and to suggest follow-up or probing questions.

In the *focus group* interviews two IPSOS representatives participated as technical support and notetakers. The focus groups lasted between 1 hour 10 minutes and 1 hour 37 minutes. The same interview guide was used as in the stakeholder interviews. However, because there were more participants in these interviews, we did not have time to cover all questions. Some participants had taken part in focus groups before, some had not, and the familiarity with video call software varied. Conducting a conversation with several people in a video call can be challenging as “talking over each other” and “taking the floor” can be both intimidating and difficult. The raise-hand function in the video call software was therefore used. By using this function, the conversation needed more facilitation than we can assume a real-life conversation would, by having to “allow” the next in line to talk. We consider this to be less engaging than conducting real-life conversations.

2.3.5 Transcribing, analyzing and reporting

Stakeholder interviews were transcribed verbatim by Winther and myself, while the focus group interviews were transcribed by IPSOS, not verbatim. The transcriptions from IPSOS were considered to be of poorer quality than verbatim transcripts, lacking detailed information about participant statements such as transitions in the conversation, which could be important for identifying whether the participants disagreed or not. Subsequently, the sound recordings were sent to a professional transcriber for verbatim transcripts. These were delivered post analysis for paper II. In paper III we have used both the non-verbatim and the verbatim transcripts. Therefore, the focus groups are termed group interviews in paper II and focus group interviews in paper III. In this thesis I use the latter term. The analysis method, however, was similar for papers II and III, and the data from the focus groups are mostly not reported nor analyzed as interactions, but as statements from individuals. Exceptions to this are found some places in paper III, where the interactions are reported in the form of *there was agreement in the group about* […].

Figure 3 shows the flow of the coding, sorting, analysis and reporting of the data sampled in the interviews. The interviews were coded post transcription in preparation for analysis. Initially, a list of codes was pre-decided based on the research questions and content of the interview guide, including *sustainability definition* and *sustainability and animal welfare*. However, as the aim of the analysis became clearer it was decided that we wanted to generate specific control questions for sustainability assessment in paper II and describe considerations and conditions for social acceptability of genome-edited salmon in paper III. I therefore revisited the material through one code, *concern*. The coded samples were then used both for paper II and III. I separated the concerns/considerations/conditions based on whether they were regarding genome editing/gene technology, societal utility, sustainability, or other factors.

The further analysis focused on identifying and condensation of meaning for both papers. The identification of statements was part of the coding process, where we identified opinions on genome editing of salmon and sustainability, and similar statements were grouped together. The approach entails that the opinions already exist in the participant, and these can be coded and condensed across all the interviews (Brinkmann & Kvale 2014, p. 223), leaving us as researchers with a list of elements containing meaning and representing the opinions of the people participating in our study.

For paper II, I mainly used statements related to sustainability, but some concerns related to genome editing in itself, and whenever societal utility also concerned sustainability, such statements were included. Induction was used to identify control questions based on the concerns. Additionally, the codes sustainability and sustainability and animal welfare, supplemented the analysis for both control questions and to use participants' perception of the concept of sustainability to inform the design of the assessment structure. Interview data was supplemented with data from document analysis as previously described, and structured and reported according to the sustainability assessment structure described below (chapter 0).

For paper III, I took the extensive list of considerations and conditions in all categories and merged them with the concerns Winther had identified in her revisiting of the transcripts. This latter cooperative part of the coding process for paper III is the reason why the paper states that both pre-decided and emerging codes were used. The process generated a quite vast list of 36 concerns and criteria for using CRISPR on farmed salmon, analyzed through induction and deduction (Brinkmann & Kvale 2014, p. 224-225). The list was then reduced to a list of 20 considerations and conditions through discussion until consensus. In paper, III we have not described the results as 20 considerations and conditions, but rather based the results and discussion on these.

The varying number of participants per stakeholder group has not had an impact on which concerns that have been emphasized in the papers. Meaning that, even though there were more participants from salmon farming than Sámi resource management, the concerns expressed by salmon farmers have not been weighted heavier in the generation of the list of sustainability topics or criteria for social and ethical assessment. Similarly, we have not considered some stakeholder groups to be more important than others. However, because some groups were presented by more people than other groups, some groups are more often represented in having concerns, which is most evident in paper II where stakeholder groups are identified for each control question. It might therefore seem that salmon farmers have more concerns than Sámi resource management, for example. The same goes with the Sámi versus the Norwegian focus groups.

Papers II and III are both based on the one same code as shown in Figure 3. This is something that was discussed several times. The main risk is to commit salami slicing or duplicate publication, where one dataset is used to generate several publications (Supak Smolcić 2013). However, in papers II and III, we ask different research questions and take on different aspects of the field, and in paper II we include other data sampling as well to supplement the social research. This is illustrated in Figure 3. Based on this, I argue that the segregation of papers II and III is sufficient to publish the two papers independently. We have also been transparent about this dual use of the interview data in the publishing processes and in the manuscripts (see Blix & Myhr 2023, p. 4).

The way in which the empirical data has been used in this thesis, to inform sustainability assessment as in paper II and the policy recommendations in paper III, is similar to the approach of empirical ethics. This is a growing field (Davies et al. 2015) where empirical data is used to inform normative analysis and conclusions (Ives et al. 2017). Here, I have not used an ethical theoretical framework, I do not conduct an ethics analysis, and I do not draw normative conclusions. My study is more descriptive than normative, and I have therefore decided not to place this thesis under the empirical ethics umbrella, however big that umbrella might be (Davies et al. 2015). Nonetheless, the data is used to inform the impact assessment and criteria related to ethical issues, as the experiences stakeholders and citizens base their statements on gives us as researchers "[…] a broader and better basis for making claims" (Winther 2022, p. 8), basing the conclusions in real-world experiences. This field has inspired the objectives of this study and is used in other parts of the project (e.g., Winther 2022).

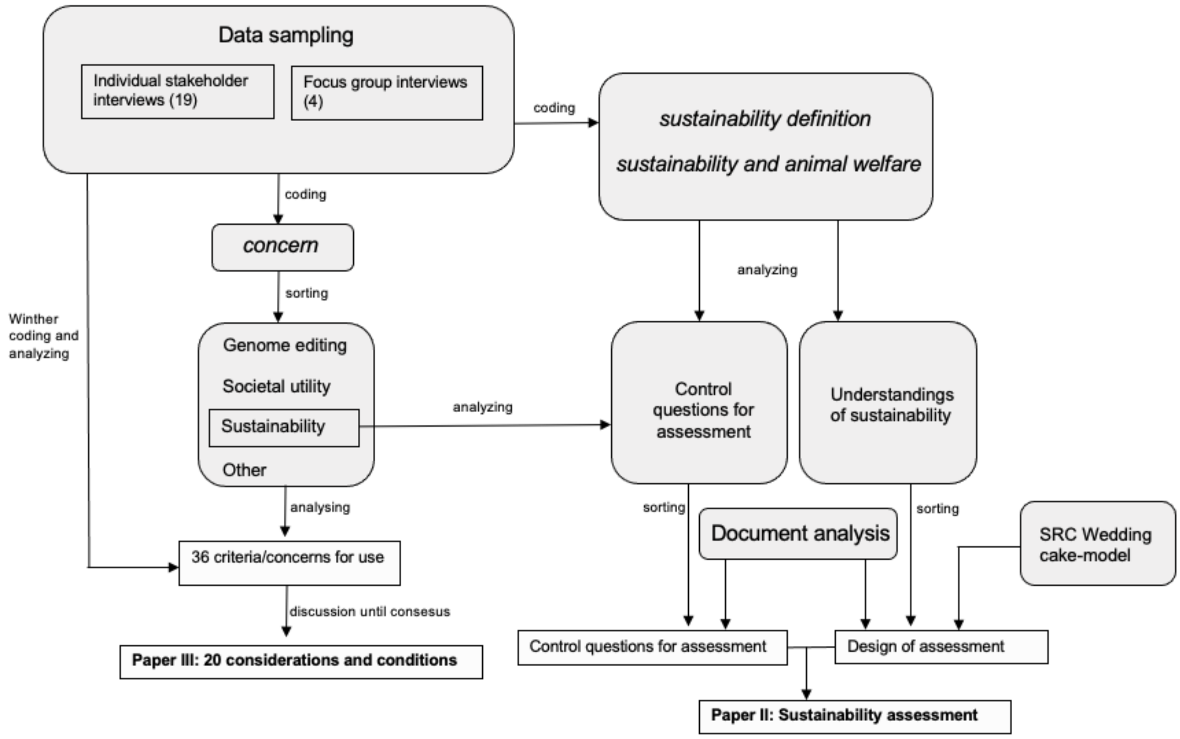

Figure 3 Flow sheet outlining the processes leading up to papers II and III. The papers are based on the same data material sampled in individual stakeholder interviews and focus group interviews. The codes concern, sustainability definition and sustainability and animal welfare were used to categorize statements before analysis and reporting. The sustainability assessment created in paper II were supplemented with a document analysis and the Stockholm Resilience Centre Wedding cake-model. For paper III, the empirical data material was analyzed in cooperation with Winther.

2.4 Making a sustainability assessment

An assessment of contribution to sustainability is required by law before a GMO can be approved for commercial use and/or release in Norway (Ministry of Climate and Environment 2005a,b). Currently, this sustainability assessment is based on six topics and respective control questions, to be used in a step-by-step and on a case-by-case basis. Previous work has shown that several additional topics and control questions are relevant and important to ask (Catacora-Vargas 2014; Gillund & Myhr 2016; NBAB 2011, 2014). As none of these have considered living modified animals, the objectives for paper II were to sketch a sustainability assessment applicable to genome-edited fish. We draw our assessment on different data, see Figure 3: empirical data from interviews, policy and strategy documents, and the Wedding cake-model of the UN SDGs (Folke et al. 2016; Rockström and Sukhdev 2016), through an inductive approach where the data is used both for the structure and content of the assessment.

Sustainability assessments are tools for decision making and policy, bridging the sustainability concept to actions (Singh et al. 2009; Waas et al. 2014). A sustainability assessment is similar to, or springs from, an impact assessment (Bond et al. 2012). In Norway, the sustainability assessment of a GMO is conducted prior to approval of commercial use (Ministry of Climate and Environment 2005a) and compares the desired objectives to the expected effects of an action (Waas et al. 2014). Sustainability assessments can be informed in different ways by science, evidence, knowledge, values, norms, interests, power relationships and institutional context (Carson 2019; Dahl 2012; Meadows 1998; Waas et al. 2014).

Indicators can be used in sustainability assessment as reference values which allows for interpreting something, indicating how far from or close to the sustainability target or goal the element is (Waas et al. 2014). Amundsen (2022, p. 3) found that the indicators in private aquaculture standard certification systems can limit the scope of sustainability if "the map becomes the terrain", where anything outside the indicator list is not considered important for sustainable development. Similarly, Meadows (1998) state that sustainability indicators can be used to measure what we value, and what is measured is also cared about.

In paper II, we focus on topics and subtopics (FAO 2014), which can be considered to come prior to indicators (de Olde et al. 2016). We identified topics and formulated control questions within the three sustainability pillars, that will open for reflection on a genome-edited salmon contribution to sustainability within a given context or topic, similar to the SAFA (Sustainability Assessment of Food and Agriculture Systems) guidelines (FAO 2014). The underlying understanding, or multiple understandings, of what sustainability is, will influence what is assessed, just as with indicators. A sustainability assessment needs to both operationalize sustainability, ensure stakeholder involvement, generate information, structure complex information and be a learning process for those involved in the assessment (Waas et al. 2014). Therefore, in paper II, we considered different perspectives and experiences by having the stakeholder and citizen interviews inform the structure *and* content of the assessment. This answers the need for a flexible assessment (Amundsen 2022), focusing on what the potential effects of introducing the genome-edited salmon in Norwegian aquaculture are, and who will be affected by it (Carson 2019).

The sustainability assessment was designed in two successive steps. The first step was published as an extended abstract (Blix & Myhr 2021). Here, we dissected the assessment currently used by the NBAB (2009), and the specific GMO crop cases elaborated previously (Catacora-Vargas 2014; Gillund & Myhr 2016; NBAB 2011, 2014), which can be considered operationalization of the original assessment guidelines (NBAB 2009). The structure of these assessments, built in lists of questions under separate headlines, was transferred into a large table to see to what degree they were already overlapping. The assessments already related to the three pillars of sustainability, as topics and control questions in the GMO crop assessments, were grouped into pillars: ecology/environment or economy/society. The official guidelines were broader and more generally spanned the pillars. Table 4 below shows how we merged the topics form the GMO crop assessments. The wording of the topics was adapted to the context of farming salmon (Blix & Myhr 2021).

Table 4 Sustainability topics in GMO assessments. The NBAB's sustainability guideline document (2009) in first column, and with relevant topics developed for specific GM crops (Catacora-Vargas 2014; Gillund and Myhr 2016; NBAB 2011, 2014) according to ecology and environment and economy and society. From Blix and Myhr (2021).

Original guideline document (NBAB 2009)	**Operationalization of guidelines: Report on plants adapted to salmon** (NBAB 2011, 2014, Catacora-Vargas 2014, Gillund and Myhr 2016).	
	Pillars	Topics
Global effects	Ecology and environment	The genetically modified organism
Ecological limits		Interaction between the GM and the environment
Basic human needs		Gene flow to wild relatives
Distribution between generations		Preservation of biological diversity in ocean and rivers
Distribution between rich and poor		Resistance in salmon to diseases and parasites
		Comparison with control salmon (farmed)
(For all core ideas: Do these effects differ between production and use?)		Safety of human health and the environment over time
	Economy and society	The right to sufficient, safe and healthy food
		Animal welfare*
		Living conditions and profitability for fish farmers and coastal communities in short and long terms
		Biodiversity and genetic resources for food and aquaculture
		Independent risk assessment
		Freedom to choose a different aquaculture system in the future

** Included regarding plants for animal feed in NBAB (2014) and Catagoras-Vargas (2014)*

Second, based on Blix and Myhr (2021) we advanced our development of the assessment, including documents and interview data. Central to the sustainability debate is *Agenda 2030,* where the 17 sustainable development goals (SDGs) were presented (UN 2015). Norway is already applying the goals in sustainability strategies such as the *Aquaculture Strategy*, where the SDGs are used as a reference for sustainable growth (Ministry of Trade, Industry and Fisheries 2021). However, *Agenda 2030* does not explain how to operationalize and quantify the goals (see e.g., van Vuuren et al. 2022) – nothing and everything is prioritized in the UN SDGs, which poses a challenge to operationalizing them (Swain 2017). In addition, the goals are "often thought of quite linearly" (Rockström & Sukhdev 2016). Therefore, Rockström and

Sukhdev (2016) introduced a reorganization of the SDGs in a Wedding cake-model where the aim was to reconnect to the biosphere through sustainable diets, based on how society and economy are subsystems within the biosphere (Folke et al. 2016). Rockström and Sukhdev show in their talk how all the SDGs can be connected to foods, or rather, that food connects all the SDGs. A sustainability assessment based on this biosphere-based sustainability perspective, could potentially ensure more long-term management of natural resources and release of genome-edited organisms, while at the same time referring to the SDGs which are a familiar context for authorities and business. When building the assessment, statements from documents (see chapter 0) and interviews (see chapter 2.3.5) were sorted into the topics environment, society, and economy, and subsequently condensed across documents and interview statements. Then the statements were written into control questions to fit the purpose of an assessment, similar to how control questions had been formulated in Catacora-Vargas (2014), NBAB (2011, 2014), and Gillund and Myhr (2016), and categorized into topics.

3 Results

In this section I summarize the main findings in papers I-III.

3.1 Paper I

In paper I, we *systematically* reviewed all research published in peer review journals between 1995-2021 on genome editing of aquaculture finfish species. We mapped the status of the research field of genome editing in aquaculture finfish connected geographical location between the research, aquaculture production and regulation of GMOs. In addition, we commented on some implications for sustainability. The resulting 56 papers were published from 11 different countries, describing 19 different species, targeting 57 different genes (and some paralogues). Further, 23 of the publications described potential relevance for or application in aquaculture. The six types of traits that have been studied are reproductive and developmental traits (28 studies, including sterility, fertility, sex determination and embryonal development), growth (10), pigmentation (8), disease resistance (7), trans-GFP (4), and omega-3 metabolism (2). CRISPR was by far the most used genome editing tool, and the most studied species groups were the tilapias, salmonids and carps, with Atlantic salmon appearing in 7 studies. We identified several technical challenges, such as off-target mutations, the effect of whole-genome duplications, and mosaicism.

Further, we found a connection between aquaculture production and research on genome editing of aquaculture species. China and Norway are amongst the top 3 countries identified in this review, in terms of number of publications, while also being the biggest producers of aquaculture and salmon, respectively (FAO 2022, p. 9, 97). It has been argued that in a process-based regulation system, fewer will have the incentives and resources to even conduct research on genome-edited organisms, because at commercialization these must be thoroughly assessed. Whether a country has product or process-directed GMO legislation does not seem to influence the research. Norway is a good example of this, considering the process-based regulation seen in relation to the research efforts on sterility in salmon.

Finally, we summed up the traits research thus far with an emphasis on contribution to sustainable development in aquaculture. Whether the traits will have the effect suggested below still needs investigation, such as whether disease resistance actually improves welfare long-term, if sterility is sufficient to avoid negative ecological impact, and whether growth enhancement might not be possible to combine with good welfare. Whether genome editing allows for intensification or maintenance of the biomass produced also needs further study, as this could lead to new, unknown threats such as undiscovered diseases or parasites.

3.2 Paper II

In paper II, we sketched a sustainability assessment framework for genome-edited salmon Table 5 modified version of the table in Blix and Myhr (2023). The paper explores perceptions of sustainability in policy documents, stakeholder interviews and citizens (focus) group interviews, in addition to concerns and criteria raised in the interviews regarding the use of genome editing in aquaculture. The framework was aligned with the UN SDGs in the rearrangement into a Wedding cake-model with a biosphere-based sustainability perspective (Folke et al. 2016; Rockström & Sukhdev 2016). There are three main findings in this paper.

First, a biosphere-focused assessment would be supported by policy documents, stakeholders and citizens. The policy documents showed some consensus on the role of nature and biosphere in sustainability, and nearly all documents referred to the UN SDGs. Nature is also the main concern amongst stakeholders and citizens, principally effects on ecology and the environment, and especially the wild salmon. Consequently, the framework can be designed according to the SDGs and the Wedding cake-model. As a first step, the assessment should identify potential threats to ecology and the environment, in terms of reduced biodiversity, change in selection pressure for pathogens in the environment, changes in production such as the type and content of feed, and the effect on the resilience of the production system and the surrounding environment.

Second, local and indigenous knowledge, traditions and rights should be included in the second step, society. The conflict between national and minorities' interests and rights is well documented in Norway and abroad, including in the case of wild salmon and fisheries versus aquaculture in Norway. The rights of the Sámi people in Norway with regard to the role of nature in their culture is legislated nationally and globally. Including a Sámi perspective in the assessment is initiated by including this topic, but an improvement would be to include Sámi representatives in the assessment process.

Third, animal welfare, health and intrinsic value should be considered part of the third economy level. Animal welfare is important for sustainability as good health and welfare means less loss of lives and thus more efficient production. In addition, a food production which respects the intrinsic value of animals and ensures good health and welfare is sustainable because this is crucial to the ethical justifiability of animal protein production now *and* in the future (Broom 2010).

Table 5 Sustainability topics identified in paper II and included in the framework for sustainability assessment of genome-edited salmon (Blix and Myhr (2023).

Level	Topics
Biosphere	**Ecology** Impact on environmental pollution (chemicals/pharmaceuticals) Climate change Resilience in food production systems
Society	Food safety, security and quality Justice and equal access Future generations access to resources Consumer and citizen engagement and acceptance **Local and indigenous knowledge, rights and traditions** Gender equality in food production Global effects
Economy	**Farmed fish health, welfare and intrinsic value** Production efficiency Available alternatives Employment and economic growth

3.3 Paper III

In paper III, we identified the main considerations and conditions in interviews with stakeholders and citizen focus groups regarding the use of genome editing in salmon farming, with the aim to identify what is at stake with regards to social acceptance of genome-edited salmon. The stakeholders and citizens were presented potential cases: sterility, lice resistance and growth or other efficiency-related traits. Comparing the stakeholder interviews to citizen focus groups, we observed that the in focus groups, people were less familiar with the topic and often reluctant to talk about gene technology. These conversations were therefore often concerning the salmon farming industry itself, and not so much the technological solution.

While several were positive towards the potential introduction of CRISPR to solve challenges in the salmon farming industry, many still hold concerns about the technology. The ability to predict unforeseen consequences, such as off-target effects, was questioned by both stakeholders and citizens. Crossing species was considered unacceptable, and avoiding this was stated as a requirement for the use of the technology. Further, the main considerations amongst both stakeholders and citizens were the protection of wild salmon and the environment, and the health and welfare of the farmed salmon. Any application of genome editing should prioritize the welfare of the farmed salmon above economic profitability, and any use of genome editing that contributes to the farmed salmon being worse off than it already is, was considered a great concern. It was also a concern, although and uncertain one, whether genome editing could be compatible with respecting the farmed salmon's intrinsic value.

Some uses of genome editing were considered more acceptable than others. Both sterility and lice resistance were considered acceptable solutions, given that introducing such salmon would not pose a negative impact on wild salmon, or lead to more intensive salmon farming. Regarding growth and efficiency, people were more reluctant about such changes, as it was not considered beneficial to either the environment or the farmed salmon.

Finally, we identified several conditions for the products and demands for the industry. If genome-edited salmon are to be introduced in farming, and on the market, people considered labelling to be important, although some pointed to labelling as problematic if one wants to separate GM from genome-editing. Social acceptance amongst the Norwegian population was considered an important criterion by several, and the availability of the product as well. Following from this, several participants also emphasized that the challenges that the salmon farming industry is struggling with are caused by the intensive monoculture. Removing symptoms of that by genome editing will not solve the issues.

4 Discussion

In the following discussion I will answer the main research question based on the findings and discussion in papers I-III where the secondary research questions were explored. Can genome-edited salmon be a sustainable and socially acceptable solution to aquaculture? First, I update the review in paper I with the most recent publications on genome editing of aquaculture finfish. Second, I discuss potential consequences to wild salmon and farmed salmon by the introduction of suggested solutions sterility and lice resistance, and comment on growth enhancement and pigment changes. Finally, I end the discussion by describing the relation between paper II and III, before moving to discuss some of the identified conditions for social acceptance of genome-edited salmon from a social sustainability perspective.

4.1 Update of paper I

The systematic literature review in paper I has been updated (16.08.22) with studies published in 2021 and 2022 using Scopus as search engine, with the extensive search string (Table 2). A total of 26 new records of empirical studies using genome editing in an aquaculture finfish species were included, see Table 6 for a summary of the results. The search shows that well-known model- and aquaculture species are still preferred, such as Nile tilapia, different carp species, and salmonids (Figure 4). The distribution of traits targeted is shown in Figure 5. Compared to paper I, there is an increase in studies investigating the genetic basis and mechanisms for coloration in both carp and tilapia. Both these species groups have varying pigmentation in their skin, which is considered an economically valuable trait, for example uniform colored fish being preferred by consumers over patching (Wang et al. 2022a). In papers I and II, we indicated that other traits such as disease resistance would contribute more directly to sustainability, depending on the actual outcome of introducing such traits. In this update, I found that fewer studies are looking at disease resistance traits, compared to paper I. Similar to paper I, the number of studies on reproduction and development is still about half of the total number of records. With regards to technical challenges of genome editing fish, several studies find that duplicated genes have different roles in the fish body (Chen et al. 2021; Mankiewicz et al. 2022; Mou et al. 2022; Wang et al. 2021a; Wang et al. 2021b). This might impact the desired end result of genome editing fish and should therefore be taken into consideration when using CRISPR for specific breeding purposes. We emphasized this in paper I as well, but the number of studies determining the roles of duplicated genes seems to have increased. All studies included in this updated version have used CRISPR, compared to results in paper I, where we identified a few studies that used ZFN or TALEN. Of the 26 new studies identified, 16 state that their objective for the research is the future application in aquaculture, with the majority of these targeting pigmentation. With regards to the countries active in this field, we found that authors affiliated with Chinese institutions are still publishing most of the studies, mostly focusing on tilapia and carp species as research animals. None of the new studies were produced in Norway. Similar reviews to paper I have been published during the last year (see e.g., Hallerman 2021; Luo et al. 2022; Roy et al. 2022; Robinson et al. 2022; Song et al. 2022; Yang et al. 2021). These reviews take different approaches, some focusing more broadly on genomic selection (Song et al. 2022), or bioinformatic tools (Luo et al. 2022), or more specifically on certain traits (Robinson et al. 2022). All conclude by emphasizing the wide potential of genome editing, while also acknowledging technical challenges that remain, such as identifying and connecting genes to traits (Roy et al. 2022), access to high quality whole genome sequences, optimizing of CRISPR delivery into eggs (Yang et al. 2021), in addition to investigation of potential negative consequences (Robinson et al. 2022).

Table 6 Empirical studies identified in an updated systematic literature search of that in paper I, presented according to the species, the objectives of the study, the trait(s) and gene(s) targeted, and the institutional affiliation of first author. The representation of the identified studies is based on Blix et al. (2021).

Species	Interest	Trait	Target genes	Institutional affiliation 1st author	Reference
Nile tilapia	Aquaculture	Pigmentation	*hps4*	China	Wang et al. 2022a
			pmel	China	Wang et al. 2022b
			csf1ra	China	Lu et al. 2022b
			slc45a2	Israel	Segev-Hadar et al. 2021
	Teleost genetics	Pigmentation	*mitfa, mitfb, gata2a, kita, kitlga, pmela, pmelb, tyrb, hps4. Gch2, csf1ra, pax7b, bco2b*	China	Wang et al. 2021a
		Reproduction and development	*cyp11c1*	China	Xiao et al. 2022
			gsdf	China	Jiang et al. 2022a
			sox30	China	Wei et al. 2022
			STaR2	China	Li et al. 2021
			dnmt3aa, dnmt3ab	China	Wang et al. 2021b
Mozambique tilapia	Aquaculture	Pigmentation	*pmel17*	Singapore	Liu et al. 2022
Red tilapia (Oreochromis mossambicus x aureus)	Aquaculture	Pigmentation	*tyrb*	China	Lu et al. 2022a
Common carp (*Cyprinus carpio*)	Aquaculture	Pigmentation	*oca2*	China	Jiang et al. 2022b
			tyr	China	Xu et al. 2022
			scarb1, scarb1-like, gch1	China	Du et al. 2021
			Mlpha1, mlpha2	China	Hu et al. 2021
			tyrp1a, tyrp1b, tyrp1c	China	Chen et al. 2021
		Growth and digestion	*mstn*	India	Shahi et al. 2022
		Reproduction and development	*cyp17a1*	China	Zhai et al. 2022
Gibel carp (*Carassius gibelio*)	Aquaculture	Disease resistance	*viperin-A, viperin-B*	China	Mou et al. 2022
	Teleost genetics	Reproduction and development	*Foxl2*	China	Gan et al. 2021
Rainbow trout (*Oncorhynchus mykiss*)	Aquaculture	Reproduction and development	*dnd*	Japan	Fujihara et al. 2022
	Teleost genetics	Reproduction and development	*sws1*	Canada	Novales Flamarique et al. 2021
		Growth and digestion	*lepra1, lepra2*	USA	Mankiewicz et al. 2022
	CRISPR as a tool	Reproduction and development	*cyp1a1* (cell line)	Switzerland	Zoppo et al. 2021
Atlantic salmon	Aquaculture	Disease resistance	*nae1, cdh1* (cell line)	UK/Scotland	Pavelin et al. 2021

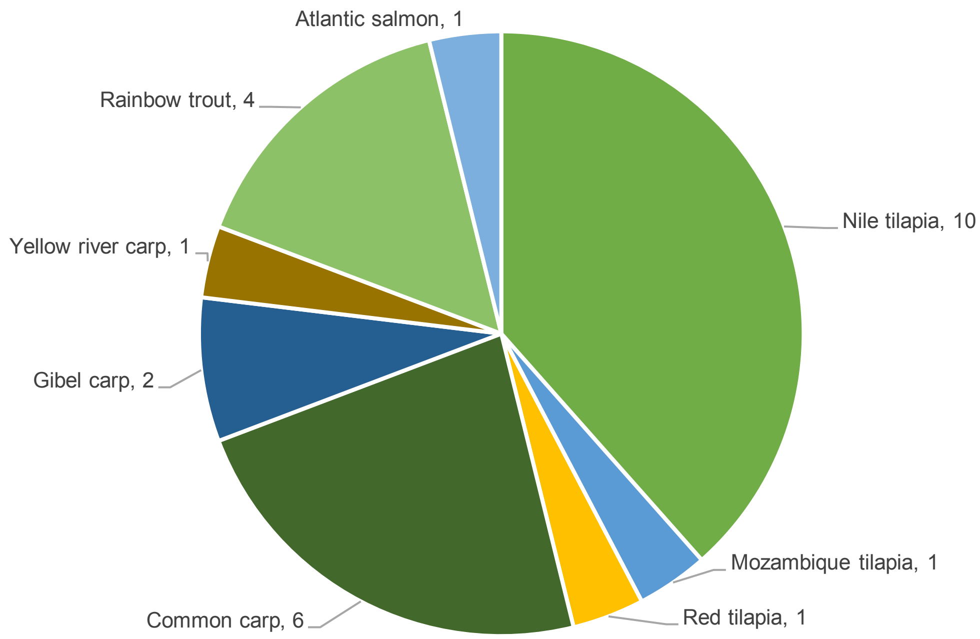

Figure 4 The distribution of species identified in the updated systematic literature review (records n=26). Number of studies using the species in question is given for each species.

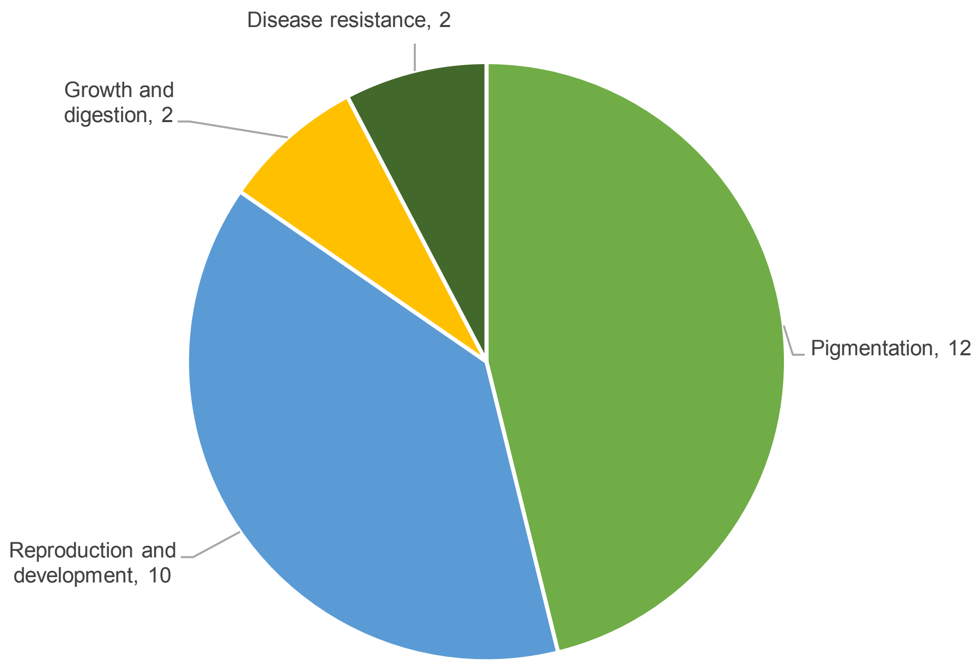

Figure 5 The distribution of traits targeted in the studies identified in the updated systematic literature review (records n=26). Number of studies targeting the trait in question is given for each trait.

4.2 Sustainability aspects of the suggested solutions: Ecology and welfare

Both in paper II and III, we show that the most general considerations made by stakeholders and citizens were regarding the impact salmon farming has on the surrounding ecology and farmed fish welfare. Genetic interference in, and the spread of disease to, wild fish stocks were also recently identified as the major hurdles for Norwegian salmon farming to expand production (Afewerki et al. 2022). According to the Norwegian Scientific Advisory Committee for Atlantic Salmon, salmon lice and escaped farmed salmon, are the two most severe threats to wild salmon, followed by climate change, physical interventions in nature and the spread of other pathogenic infections from salmon farming (Thorstad et al. 2022, p. 12). In this section I discuss potential implications of two of the proposed applications of genome editing presented in the interviews, sterility and lice resistance, in light of environmental sustainability and fish health and welfare. The application of genome editing to change pigmentation and enhance growth in aquaculture is also discussed. Most of section 5.2.2 was developed as an exam essay in BIO-8028 at UiT.

4.2.1 Sterility

When the farmed salmon escape, this poses a threat to wild salmon. In addition, it represents an economic loss for the fish farmer, especially if the escape incident in question also leads to legal sanctions. Føre and Thorvaldsen (2021) have analyzed the main technological (e.g., equipment failure) and human (e.g., competence, performance ability, communication) reasons for escapes between 2010-2018. During this period, the percentage of escapees relative to the total number of farmed salmon has declined from 0,45% in 2006 to 0,05% in 2019 (Føre & Thorvaldsen 2021). Previous to this, a similar decline in escapees was identified by Jensen et al. (2010), who argued that this was a result of a technological rearming because of stricter regulation.

Little is known about the consequences of the escape of sterile salmon into the environment. This was emphasized by study participants from wild salmon management. The sterile salmon are often promoted as a solution, as this salmon is incapable of breeding with wild salmon if they escape. A wild salmon management participant pointed out that we do not know how the sterile salmon will behave when they meet the wild salmon. Bradbury et al. (2020) have mapped how both interbreeding and other non-recombinational interactions between farmed and wild salmon can have negative effects on the latter, such as competition for resources, and transfer of disease and parasites. This was also commented in paper II. Previous studies on the triploid salmon have shown that some sterile salmon are able to return to rivers (Cotter et al. 2000) and that some develop mating behavior (Fjelldal et al. 2014). Recently, the performance, health and welfare of the genome-edited sterile salmon from parr stage to harvest size (5 years) was studied (Kleppe et al. 2022). The KO mutation of the gene *dead end* hinders development of germ cells in both females and males, and therefore also maturation and puberty. The genome-edited sterile salmon is therefore different from the triploid salmon which matures (Fjelldal et al. 2014). A challenge in this regard will be to optimize the genome editing so that all offspring are sterile. Current experiments have shown that the genome-editing also create mosaic salmon with partly developed gonads (Kleppe et al. 2022). Further, the impact of an escape event with non-sterile farmed fish is further closely associated to proximity to salmon rivers, and the size of the escaping population in relation to the wild populations (Diserud et al. 2022; Karlsson et al. 2016). Sterility should therefore be combined with other management measures, such as physical hindrance and larger marine protected areas in proximity to salmon rivers, could reduce the potential non-recombinational effects of escapees (Bradbury et al. 2020; Diserud et al. 2022; Jensen et al. 2010).

In addition to the potential ecological aspects of sterile salmon, several study participants in the interviews questioned how the sterility would affect the welfare of the salmon. This was especially a topic of discussion in one of the focus groups. While it can be discussed whether denying salmon to reproduce at all is respectful treatment of it as an animal, the lack of maturation in the genome-edited sterile salmon can be a positive contribution to farmed fish welfare as it impairs the health condition of the salmon (Iversen et al. 2016). The health and welfare study of the sterile salmon used first generation (F0) sterile, germ cell free salmon reared together with WT non-edited control salmon. The study of welfare was mainly measurements of stressors. The study found that after postsmolts had been transferred to sea water, some stress factors which can affect the ability of the fish to adapt to the new conditions, were higher in the genome-edited compared to the WT salmon. These differences had evened out after 6 months in sea water, while at harvest size, WT salmon showed higher concentration of lactate in the plasma (a stressor) than genome-edited salmon. The study concluded that the genome-edited sterile salmon were not more stressed than WT salmon (Kleppe et al. 2022). However, the growth might be a challenge as the sterile salmon had a slightly slower growth in the last part of the production cycle, a challenge that I will return to after a discussion of lice resistance.

4.2.2 Lice resistance

Salmon lice infection is among the major health and welfare issues in the farming of salmon in Norway today. The lice are causing reduced welfare for the salmon, as do the treatments used to remove them (Nilsson et al. 2019; Sommerset et al. 2022; Torrissen et al. 2013). The salmon louse is a natural marine ectoparasite residing in the Northern Hemisphere oceans, specialized to genera Salmo, Oncorhynchus and Salvelinus, with varying compatibility and encounter (Hamre et al. 2019; Klemetsen et al. 2003; Torrissen et al. 2013). The life cycle of the louse is in three stages. First a free-living stage in the water in which the lice larvae can be transferred horizontally at high host densities such as in and between salmon farms. Then follows two parasitic stages living on the salmon body, where the lice feeds on salmon mucous, epidermal tissue and blood (Fjelldal et al. 2019; Hamre et al. 2013, 2019; Heggland et al. 2020; Jevne et al. 2021). The infestation leads to stress, anemia, reduced osmoregulation and, at high infection intensities, death (Fjelldal et al. 2019; Wagner et al. 2008). Dempster et al. (2021, p. 243) argue that farmed salmon are "[…] the reproductive engine for the lice population [in Norway]". They estimated that 97,1% of all adult female lice were living on farmed salmon, which therefore have a higher selective pressure on salmon lice than wild salmon.

Unlike the Atlantic salmon, the Coho salmon (*Oncorhynchus kitusch*) and Pink salmon (*Oncorhynchus gorbuscha*) residing in the Pacific ocean, are highly resistant to the (Pacific) salmon lice. Recently, a project was initiated to take the Pacific salmon resistance mechanisms and transfer it to the Atlantic salmon – either by transferring genes, or by identifying and editing such genes already present in the Atlantic salmon genome. If the salmon is to be genome-edited to achieve lice resistance, this will presumably be by making the salmon either highly or fully resistant. The *highly* resistant salmon will encounter the lice, but have an improved immunological response to the lice infections, reducing the negative impacts of infections, and possibly fighting some of the immunomodulatory responses of the lice, reducing the compatibility (Coates et al. 2021; Nofima 2021b). Such a highly resistant salmon will still be able to some degree to carry and disperse parasites. This might lead to parasite spill-over to wild stocks. In addition, because there is an encounter between the lice resistant salmon and the lice, adaption to the resistance mechanisms could be induced in the salmon lice. The *fully* resistant salmon will potentially be edited in the release of chemical attractants (Devine et al.

2000). Thereby, encounter between farmed salmon and lice is avoided, or at least the salmon is repelling the lice before it attaches to its skin (Nofima 2021b). Such a fully resistant salmon will therefore not carry lice, and therefore escaping salmon could have a competitive advantage over other salmonids by not being infected by the lice. However, both the highly and the fully resistant salmon will facilitate a strong selection pressure on the lice. The salmon lice are known for rapid adaption to changes in and around their hosts. Studies have already shown that in areas with more intensive salmon farming, salmon lice are more efficient at producing offspring, have higher infection rates, and cause more severe skin damage (Mennerat et al. 2017; Ugelvik et al. 2017). Following a former attempt to control lice in the sea cages, resistance in the salmon lice against chemical treatments appeared only a few years after the treatments came into use (Aaen et al. 2015; Coates et al. 2021; Kaur et al. 2015). Even lice with resistance against several chemicals at once have been sampled in aquaculture intensive areas (Fjørtoft et al. 2021). More research on resistance development in the lice to different treatment methods and measures such as genome-edited induced resistance is still needed (Coates et al. 2021).

This experience and concern with the issue of rapid adaptation in salmon lice was also raised by one of the wild salmon managers in our interviews. In light of the potential ecological effects of lice resistance in farmed salmon, it is arguably a potential wrong turn to focus only on removing the negative symptoms of animal farming if this is not also combined with other measures. The genome editing tool has shown promising results thus far, and knowledge about potential applications to different challenges is continuously growing. If the production system is also enhanced, by mechanical preventative measures reducing the encounter between salmon and lice, resistance could be *supplementing* these measures as a means to improve the welfare of the salmon Coates et al. (2021). The alternative treatments used today does not only induce resistance in the lice. Other immediate treatments such as mechanical brushing is actually causing higher mortality and impaired welfare of the farmed fish in comparison to the salmon lice infestation (Sommerset et al. 2022, p. 36-37). Consequently, if genome editing can be applied without causing adaptive devleopment in the lice, it holds the potential for improving salmon welfare, and thereby contributing to more responsible animal protein production.

4.2.3 Pigmentation and growth

Then there are some traits, such as pigmentation and growth, which does not necessarily contribute directly to more environmentally sustainable salmon farming or improved fish health and welfare. Furthermore, growth is already well implemented into the salmon breeding program (Solberg et al. 2013; Thodesen & Gjedrem 2006). Still, it is interesting to discuss some implication and potentials of these traits considering that targeting of these traits in genome editing is heavily studied globally (Blix et al. 2021; Hallerman 2021), and the only commercialized genome-edited fishes have been edited for increased growth.

Loss of or changed pigmentation can be useful when farming fish, either as a visual tool to separate edited and non-edited fish from each other, or as a commercial trait (see e.g., Liu et al. 2022; Lu et al. 2022a,b; Segev-Hadar et al. 2021; Wang et al. 2021a; Wang et al. 2022b). However, removing the pigmentation in fish can have welfare and behavioral effects (Slavík et al. 2016; Wang et al. 2022a). The physiological and behavioral effects of changed pigmentation in fish have barely been mentioned in any of the studies that have used genome editing to change the body and eye color of carps and tilapia. Wang et al. (2022a) found that pigment-free tilapia preferred more shallow areas, and the authors suggested this to be caused by light sensitivity. This the only study of those identified in paper I and in the update that mentions such changes in behavior. Ocular pigmentation changes such as albinism are identified in other studies where, for example pigment genes *slc45a2* or *slc24a5* have been knocked out in species such as tilapia (Segev-Hadar et al. 2021) and mackerel tuna (Pandey et al. 2021). Wang et al. 2022b also identified a change in eye pigmentation in both single and dual homozygous tilapia *pmel* KO mutants. They did not report whether they had investigated light sensitivity, only that "overall performance and behavior of the mutants were not influenced" (Wang et al. 2022b). When targeting pigmentation, either as a tool or because of commercial value, ensuring good fish welfare should be closely followed up.

In some of the Norwegian studies identified in paper I, pigmentation has been used to visually trace successfully edited sterile individuals by having the KO of *dnd* in concert with a KO of *slc45a2* – a pigment gene (Edvardsen et al. 2014; Wargelius et al. 2016). The genome-edited sterile salmon studied for health and welfare by Kleppe et al. (2022), also had a KO of *slc45a2*. The authors emphasize that other effects of the *slc45a2* KO cannot be excluded. The salmon´s vision was not commented on, and it was not reported whether the WT salmon had advantages over the genome-edited salmon (Kleppe et al. 2022). The pigment loss will probably not be used in commercial production, as this changes the whole look of the salmon, which could pose a challenge with regards to consumer preferences. But in research it is still a useful trait, albeit a potential welfare issue. Therefore, the phenotypic effect of KO in pigment-related genes should be considered on a case-by-case basis, as it may vary with species and the gene in question (Slávik et al. 2016).

Growth enhancement is the only genome editing solution applied thus far in commercial aquaculture. In a recent opinion paper in Reviews in Aquaculture, Hallerman et al. (2022) reviewed that eight species have been used in research on growth and muscle development, such as common carp (Shahi et al. 2022), channel catfish (Kahlil et al. 2017), blunt snout sea bream (Sun et al. 2020) and olive flounder (Kim et al. 2021). In comparison, research on disease resistance has included fewer species, and these studies are often still at cell line level (Blix et al. 2021; Hallerman et al. 2022). With regards to the market, the three fishes approved for commercial use, all (presumably) have a KO of *mstn*. This is a gene which regulates myostatin differentiation in skeletal muscle cells, and therefore KO results in increased muscle growth (Khalil et al. 2017). One of the approved genome-edited fishes is a tilapia exempted from GMO regulation in Argentina on the basis of absence of transgenesis (Evans 2018). Allegedly, this tilapia has higher fillet yield compared to WT tilapia. It is not openly available what gene(s) have been edited, but the producer Intrexon Corporation holds a patent on tilapia with enhanced growth characteristics, where the gene *mstn* has been knocked out (Callura and Peterson 2019). In Japan, the tiger puffer fish (*Takifugu rubripes*), and red sea bream (*Pagrus major*) were both mutated in the *mstn* gene, as previously demonstrated in several studies (e.g., Khalil et al. 2017; Shahi et al. 2022). Similar to the process in Argentina, the Japan Ministry of Health, Labor and Welfare considered these fishes as not GMOs and have approved them for commercialization (Loew 2022; Normile 2019).

Increasing growth could potentially have a positive impact on aquaculture as it increases the value of each individual fish (depending on production costs), and thus makes the value-creation more efficient per volume unit. It could reduce the rearing time if genome-edited fish reach slaughter weight faster than conventionally bred fish, and it may therefore also improve the utilization of feed. As mentioned above, Kleppe et al. (2022) found that the genome-edited sterile salmon showed slower growth rate towards the end of the production cycle compared to the WT salmon. This trait was explained to be different expression patterns of *gh2,* a paralogue to *growth hormone* gene. The study concludes that the genome-edited sterile salmon is similar to the WT salmon, but that the former might require increased cultivation time at sea to reach the desired slaughter weight. This might pose as a challenge because longer time at sea increases both the chances of escaping and exposure to infections and parasites such as the lice. Furthermore, it increases the use of feed which the main cost category to, and least climate friendly parameter of, aquaculture (Albrektsen et al. 2022). In theory, this reduced growth of sterile genome-edited salmon could be countered by combining KO of *dnd* with KO of *mstn*.

However, increased, or more intensive, growth comes with welfare issues. Historically, reducing the time at sea and increasing growth rate have been the main priorities in the Norwegian salmon breeding program (Thodesen & Gjedrem 2006). This has been difficult in a welfare perspective, as fast growth in juvenile and smolt land-phase have shown to be negative for heart development (Frisk et al. 2020). Similarly, there are, concerns related to increased growth of fish. In the interviews, we often presented the case of increased growth to the study participants because this is a very specific and visible example of genome editing. Several of them considered that to be less relevant for the Norwegian salmon. However, amongst participants from the salmon farming industry, this view varied; some considered it to be a positive suggestion, while others had negative associations with chickens bred for increased growth. A fish health worker expressed concern regarding growing pains and spinal deformities. The reported effect on welfare following KO of *mstn* varies from identifying deformities (Zhong et al. 2016) to finding no significant differences between edited and non-edited fish other than the expected increased growth (Shahi et al. (2022). Similar studies should be conducted, and the health and welfare indicators could be expanded to ensure that there are no negative impacts on health or welfare by KO of *mstn*, or other growth enhancing mutations.

4.3 Sustainability and social acceptability

Papers II and III are based on the same data material, but the research questions asked are dissimilar. In paper II, we identified some important social sustainability topics for genome-edited salmon. Only the topic of local- and indigenous peoples was elaborated on in this paper. Paper III explored societal acceptability more broadly by identifying conditions for social acceptance amongst stakeholders and citizens. The conditions we identified in paper III further elaborate on several of the sustainability topics identified in paper II, with the most widely shared considerations among study participants being effects on wild salmon and the welfare of farmed fish. These are again closely associated to sustainability, as shown in the previous section and in paper II where we organized these concerns to the biosphere and economy level, respectively. Papers II and III are therefore intertwined, while at the same time elaborating on different aspects of sustainability. Here I elaborate on the social acceptance of genome-edited salmon, and demonstrate one way in which sustainability and social acceptability is connected in the context of genome-edited salmon.

The conditions identified in papers II and III were often directed not towards the genome editing technologies specifically, but rather towards how genome editing might amplify challenges already present in salmon farming in general. Similar findings have been presented in previous study of social acceptance of GMOs (Hviid Nielsen 2007b). This is elaborated on with an emphasis on ecological effects and fish welfare above. Furthermore, there are some limits in our study which concern the challenge of talking to people about something that does not yet exist – a genome-edited salmon being farmed and commercialized. This was especially difficult in the conversations where people did not have any knowledge about genome editing. Altogether, it was found to be difficult to assess genome editing as a solution in aquaculture without also questioning the systemic challenges that Norwegian aquaculture entails. The conditions for social acceptance of genome editing in salmon farming might therefore depend on the social acceptance of salmon farming.

There are different lines of research and debates that consider the social acceptance of salmon farming. Alexander et al. (2020) state that research on the social dimension of sustainability in aquaculture is lacking. Social sustainability can be framed in different ways, one being the concept of *social license to operate* (SLO) (Alexander et al. 2020). Originally used for the mining industry, today this concept is applied to other industries as well, such as aquaculture (Mather & Fanning 2019). SLO implies that a society should have trust in or show approval of, the activity of a company or an industry (Moffat et al. 2016). Other have also described SLO as a "social contract between operations and society" (Crowther and Seifi 2018, as cited in Alexander et al. 2020, p. 62), and SLO is more informal than regulations and official policy. Today, the SLO of aquaculture is affected by several factors identified in different studies, with one of these being the "distribution of benefits" (Alexander et al. 2020).

The distribution of benefits has also previously been shown to be an important condition for social acceptance of GMOs (Frewer et al. 2004; Gaskell et al. 2000). Several relationships where interests might conflict are present in our study, and such potential conflicts can appear if either environmental, social or economic sustainability is prioritized. The framework proposed in paper II uses a biosphere-based sustainability perspective (Folke et al. 2016), suggesting that nature should be prioritized. While the intention of this perspective is to ensure that the life-support system is preserved, a consequence might be that the social and economic dimensions are not equally considered if the framework is not used with flexibility. Elkington (1998, reviewed in Alexander et al. 2020) famously proposed the business-oriented concept of the triple bottom line as a way to balance environmental, social and economic aspects in the activity and outcomes of a corporation. The idea is that society is dependent on the economy, which is dependent on the environment, and balancing the dimensions would allow corporations to measure their impact on environment and society. This concept has been criticized for being static, and governance has been suggested to be added as the fourth dimension (Alibašić 2017).

The most evident application of genome editing with skewed distributions of benefit is that of growth enhancement. When presented with this solution, the study participants almost exclusively argued that this would be only for the benefit of humans, and more specifically for the profit of the industry. The Norwegian aquaculture activities are already causing a conflict between the protection of nature, which aquaculture threatens, and the value creation it generates. Today, the social responsibility in terms of effects on local communities and consideration of indigenous interests is also shown to be lacking in assessments of aquaculture, such as in the private certification standards (Amundsen & Osmundsen 2018; Brattland et al. 2021). Genome editing could help alleviate this conflict if solutions such as sterility and disease resistance are applied because they reduce the negative impacts on ecology, depending on the actual outcome of the application as discussed above. However, if the effect of removing the "symptoms" of salmon farming is an increased, more intensive monoculture of salmon, society might perceive the genome editing as only beneficial for the industry, not the fish nor society in general. This indicates that genome editing might not be a 2silver bullet". The way it is applied, and the potential effects it can cause such as intensified production, reduced welfare, or continuation of escapees, will determine its commercial success. Thus, genome editing will not make salmon farming more sustainable alone, even though it can contribute to less negative environmental impact and improved fish health. In addition to researching the potential of genome editing to answer *some* requirements, such as reduced environmental impact and improved animal welfare, salmon farming should strive for producing fish in a smarter manner, on fish´s premises, and in cooperation with, not fighting against, nature, to be sustainable and socially acceptable.

5 Further work

In light of the discussion above, I end this thesis with some brief reflections on potential tasks for further work and alternative solutions.

The findings in paper II and III shows that discussing applications of genome editing in food production might be very context depended, which suggests more cases showing a variety of uses of genome editing and contexts needs to be explored. As a further exploration of conditions for social acceptance of genome-edited fish in aquaculture, case-by-case studies of different species and traits should be continued. The cases chosen to be used in the interviews were based on the findings in paper I in addition to recent projects that have not yet published research. Since paper I did not cover all species and all traits of fish aquaculture, other cases could have been interesting to explore in future interviews. One case in particular, which is also likely to be applied is the sterile, germ cell free, salmon used as a recipients of donor germ cells – a surrogate solution (Jin et al. 2021). One of the main challenges of genome editing is mosaicism. One solution is to use genome editing to create surrogates which can carry transplanted non-mosaic germ cells that have been edited and grown in controlled environments *in vitro*. Jin et al. (2021) have even pointed to surrogacy as a potential prerequisite for scaling up the production of genome-edited fishes to avoid having mosaic fishes, and recent research has already initiated this work (see e.g., Fujihara et al. 2022). Presumably, other considerations and conditions would have been raised in the interviews if we asked about opinions on using genome editing to create, or requiring, surrogate fish carrying genome-edited eggs. Therefore, in future research on sustainability and social acceptance should include other applications of genome editing than those used in our study, such as sterility to generate surrogates, or behavioral traits such as swimming ability (Higuchi et al. 2019), and increased appetite Mankiewicz et al. (2022). The endless possibilities of genome editing in changing animals traits also suggests that regulation should be case-by-case, an aspect which also should be further explored.

Further, the various considerations and conditions identified in papers II and III also suggests that the non-safety criteria in the Norwegian GTA are useful for identifying conditions for social acceptance of particular genome-edited organisms. The many considerations regarding salmon farming in specific, which we identified, also indicate that it could be useful to apply such criteria for assessment of intensive culture of animals in general. Findings in papers II and

III also indicate that present approaches for sustainability assessment of aquaculture present needs optimization, as previously suggested by Amundsen (2022).

Above I argue that genome editing holds the potential to solve some sustainability issues present in the salmon farming today, but not all. Another approach to the sustainability assessment, and to further develop the framework, could be an analysis of resilience where the whole production cycle and all stakeholders are taken into consideration. Resilience describes how a system can withstand stress over time, "and to keep functioning in much the same kind of way", by identifying tipping points and when these will be crossed (Walker 2020, p. 1). Analyzing the effects of introducing genome editing in salmon farming through a resilience lens could allow for further exploration of the connection between aquaculture and other activities along the coast. Following from this, it could also be interesting to investigate the suggested planetary boundary for novel organisms such as GMOs (Steffen et al. 2015). Even though GMOs are not representing a planetary system on their own, such an analysis could consider different GMO cases, and comparison of GMOs to non-GMO varieties, or to invasive, or exotic, species (Jeschke et al. 2013). On this basis, one can determine the resilience of ecosystems in handling these organisms, with special emphasis on the effect of introducing novel traits.

Finally, further research should also be diverse in its exploration, identification and discussion of the complex problems use of genome editing is raising. It is evident that scientific fields are strongly influenced and directed by their history and rules and norms for generating knowledge (Haraway 2015). Interdisciplinarity has been an important part of this thesis, in itself and as part of a larger project. Knowledge pluralism opens for different views on the same issues, and seeing the world through different lenses is needed to handle the various aspects of the complex issues food production implies. Therefore, further research should also include investigation of how to employ inter- and transdisciplinary methodological approaches which involves stakeholders and fosters qualitative and quantitative co-creation for generation of knowledge.

6 Conclusion

This thesis, including papers I-III, has explored the technological possibilities, sustainability issues and social acceptability of genome-edited salmon in Norwegian aquaculture. The range of technological possibilities is broad. Globally, we see that research is more focused on production traits such as growth and pigmentation, while in Norway research is specifically directed to environmental and welfare issues of salmon farming. The sustainability of a genome-edited salmon can be assessed according to the SDGs, and following the Wedding cake-model from SRC, one can also align the assessment according to a biosphere-based sustainability perspective, which is to ensure a long-term assessment prioritizing nature. Finally, conditions for social acceptance of genome editing are related to the technology itself and uncertainty connected to possible unintended consequences, in addition to considerations for wild salmon viability and farmed salmon welfare, which are main sustainability issues of salmon farming today. Following from the latter, the social acceptance of genome-edited salmon will depend on the social acceptance of salmon farming in general. Here I have shown that the question of applying genome editing in salmon farming is as complex as, and tightly intertwined with, the salmon farming process itself. Even though beneficial solutions that reduce environmental impact and improve animal welfare are proposed, people's reluctance to embrace the technology completely might be grounded in a fundamental skepticism about the aquaculture industry, and not as much a skepticism about the genome editing technology itself. Consequently, genome editing should not be considered a solution alone, but as one option together with other initiatives to make aquaculture more sustainable and socially acceptable.

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Appendix 1

Torill Blix
UiT – The Arctic University of Norway

List of papers and contributions (co-author statements)

Name of candidate: Torill Blix

Papers
The following papers are included in my PhD thesis:

I: Blix, T. B., Dalmo, R. A., Wargelius, A., & Myhr, A. I. (2021). Genome editing on finfish: Current status and implications for sustainability. *Reviews in Aquaculture*, 13(4), 2344-2363. doi: 10.1111/raq.12571

II: Blix, T. B., & Myhr, A. I. (2023). A sustainability assessment framework for genome-edited salmon. *Aquaculture*, 562, 738803. doi:10.1016/j.aquaculture.2022.738803

III: Blix, T. B., Winther, H., Myhr, A., Myskja, B., Holm, L. Social acceptance of CRISPR in salmon farming industry: what is at stake? (*submitted manuscript*)

Contributions	Paper I	Paper II	Paper III
Concept and idea	TB, AM, RD	TB, AM	TB, HW, BM, AM, LH
Study design and methods	TB, AM, RD, AW	TB, AM	TB, HW, BM, AM, LH
Data gathering and interpretation	TB, AM	TB, AM	TB, HW, LH
Manuscript preparation	TB, AM, RD, AW	TB, AM	TB, HW, BM, AM, LH

TB Torill Blix, **AM** Anne Myhr, **RD** Roy Dalmo, **AW** Anna Wargelius, **HW** Hannah Winther, **BM** Bjørn Myskja, **LH** Lotte Holm.

With my signature I consent that the above listed articles where I am a co-author can be a part of the PhD thesis of the PhD candidate.

Signatures from all authors must be provided.

Torill Blix, 24.11.22
Torill Blix, date

Anne I Myhr, 24.11.2022
Anne Myhr, date

Hannah Winther, 24.11.2022
Hannah Winther, date

Roy A Dalmo
Roy Dalmo, date

Anna Wargelius 08.12.2022
Anna Wargelius, date

Lotte Holm 24.11.2022
Lotte Holm, date

Bjørn K. Myskja 24.11.22
Bjørn Myskja, date

Appendix 2

Interview guide

English translated version.

Introduction: Researchers name and affiliations, a simple description of what genome editing is (e.g., “gene scissor”) and some examples (sterility, lice resistance, growth). Aim of the project is conditions for moral and social acceptance. Data is stored according to agreement with NSD, and will be used for scientific publications. Conversation will be following a three-split structure, and it is audio recorded.

Stakeholders: Participant is asked to tell about him/herself.
Focus groups: Round with names, where they live and e.g., what they do.

1 Virtues and relationship to the salmon

- What is your relationship with salmon?
- What kind of interaction do you have with salmon in your own profession? Can you describe how you handle it?
- What do you feel is your responsibility towards the salmon?
- What conflicts or challenges do you see in your own everyday work when it comes to looking after the salmon's welfare?
- What does animal welfare mean?
- Are you familiar with the Animal Welfare Act?
- According to section 3 of the Animal Welfare Act, all animals have intrinsic value regardless of whether they are useful to us. What does it mean to take this intrinsic value into account with regard to the salmon?
- What is good treatment of salmon?
- How do we know if the salmon is doing well or not?
- Is salmon treated differently from other animals we eat, such as cows or pigs? If so, what are the differences? Should there be a difference?

2 Genome editing

- What do you think about the use of genome editing on salmon? What are the possible benefits of adopting the technology? Do you have any concerns, and if so, which?

- Do you know the difference between older and newer gene technologies that can/are used in breeding? [Explain the differences between gene editing and older gene modification. Explain that these are regulated in the same way in the EU, and for now also in Norway.]
- Would you distinguish between these in terms of what you would accept?
- How do you assess genome editing and traditional breeding against each other? Is one more natural than the other?
- We talked earlier about the intrinsic value of the salmon. Does the use of genome editing come at the expense of this intrinsic value?
- (When have we changed salmon so much that it becomes a different species? Farmed salmon and wild salmon, for example, are quite different.)
- Do we have different responsibilities for farmed salmon and wild salmon?
- Is it wrong in itself to change the characteristics of salmon by genetic modification or genome editing? Why?
- What is the acceptable area of use, and what is not?
- Will the use of genome editing be within what you consider to be natural breeding?
- Considering other alternatives that exist such as [marker-assisted] breeding, can you think of arguments for why genome editing adds something new?
- Will the use of genome editing affect animal welfare? If so: How?
- Do you have examples of changes that will provide better welfare?
- How do you think consumers and the food chains will react if genome editing is used to make genome edited salmon? Do you think they will be positive about the product?
- What about yourself?/Would you buy genome edited salmon if you found it at your local supermarket?

3 Sustainability. [According to the Genetic Engineering Act, a prerequisite for using the technology is that in addition to being ethically sound, the use, or the product that is made, must also be sustainable and beneficial to society. Sustainability is assessed with regard to both the production and the use of the product.]
[Sustainable development can mean that development must take place in a way that satisfies today's needs without coming at the expense of future generations. Considerations for the environment, economy and social conditions must weigh equally heavily. The dimensions relevant to Norwegian salmon production are global impacts, ecological limits, basic human

needs, distribution between generations and economic growth. With the given description of what sustainable food production entails and requires. *This part was later removed*.]

- What do you think is/is not sustainable about current salmon production?
- What do you think will be required for the entire production to be sustainable?
- Will genome editing be able to play a role in this context? Benefits? Concerns?
- We have not mentioned animal welfare in connection to sustainability, but this may well be an important aspect. How would you assess animal welfare in relation to sustainability?
- What do you mean personally?
- Are there any specific solutions/changes to the salmon that could contribute to better/worse sustainability?

Appendix 3

Notification form / Genome editing - a game-changer in aquaculture: Conditions ... / Assessment

Assessment of processing of personal data

Reference number	Assessment type	Date
707095	Standard	08.04.2021

Project title
Genome editing - a game-changer in aquaculture: Conditions for social and moral acceptance (CRISPRsalmon)

Data controller (institution responsible for the project)
Norges teknisk-naturvitenskapelige universitet / Det humanistiske fakultet / Institutt for filosofi og religionsvitenskap

Joint data controllers
GenØk – Senter for Biosikkerhet

Project leader
Bjørn Kåre Myskja

Project period
01.05.2019 - 01.01.2023

Categories of personal data
General
Special

Legal basis
Consent (General Data Protection Regulation art. 6 nr. 1 a)
Explicit consent (General Data Protection Regulation art. 9 nr. 2 a)

The processing of personal data is lawful, so long as it is carried out as stated in the notification form. The legal basis is valid until 01.01.2023.

Notification Form

Comment
NSD har vurdert endringen registrert 07.04.2021.

Det er vår vurdering at behandlingen av personopplysninger i prosjektet vil være i samsvar med personvernlovgivningen så fremt den gjennomføres i tråd med det som er dokumentert i meldeskjemaet med vedlegg den 07.04.2021. Behandlingen kan fortsette.

Det har blitt lagt til et utvalg som består forbrukere. Videre har det blitt lagt til et utvalg som består av samiske befolkningsgrupper. Av den grunn er det nå tatt høyde for at datamaterialet vil inneholde opplysninger om etnisk oppfatning.

OPPFØLGING AV PROSJEKTET
NSD vil følge opp underveis (hvert annet år) og ved planlagt avslutning for å avklare om behandlingen av personopplysningene er avsluttet/pågår i tråd med den behandlingen som er dokumentert.

Lykke til med prosjektet!

Kontaktperson hos NSD: Tore A. K. Fjeldsbø

Tlf. Personverntjenester: 55 58 21 17 (tast 1)

Appendix 4

Invitation to participate in research project

”Genome editing – a game-changer in salmon farming: Conditions for social and moral acceptance (CRISPRsalmon)”

This is a request to participate in a research project that investigates the ethics of using genome editing tools in salmon farming. In this letter, we give you information about the goals of the project and what participation will mean for you.

Purpose
The project *Genome editing – a game-changer in salmon farming: Conditions for social and moral acceptance (CRISPRsalmon)* is an interdisciplinary research project in collaboration between the Department of Philosophy and Religious Studies at NTNU in Trondheim and GenØk - Center for Biosafety in Tromsø. The project examines ethical issues related to the use of genome editing in salmon farming and asks which social and moral conditions must be met for such technology to be acceptable. More specifically, the project considers the genome editing tool CRISPR. CRISPR is a tool that makes it possible to go straight into the DNA of the salmon and make small point changes: specific genetic material can be removed or inserted. The Institute of Marine Research has already used the technology to develop a sterile salmon. Sterile salmon can prevent one of the biggest problems in the industry, namely that escaped farmed salmon mates with wild salmon. Other possible uses are to make salmon resistant to diseases and parasites such as salmon lice, increase omega-3 levels, and make salmon better able to digest plant-based feed. In an assessment of new technology such as CRISPR, it is important to ask whether such specific applications of the technology contribute to sustainable and ethically sound development.

You can read more about the project on our website <https://www.ntnu.edu/crispr-salmon>.

Who is responsible for the research project?
Professor Bjørn Myskja at the Department of philosophy and religious studies at NTNU in Trondheim is responsible for the project. Director Anne I. Myhr at GenØk - Center for Biosafety in Tromsø is co-chair. Interviews will be conducted by PhD students Hannah Monsrud Sandvik (NTNU) and/or Torill Blix (GenØk).

The project collaborates with the Institute of Marine Research in Bergen, the University of Copenhagen, the Norwegian Biotechnology Advisory Board, Norwegian Industry, Akvaplan-niva, and researchers at the University of Veterinary Medicine (Vienna) and Wageningen University. The project is funded by the Research Council of Norway's program Aquaculture 2 - Large program for aquaculture research, project number is 295094.

Why are you asked to participate?
To answer the project's research questions, we will interview people with different roles in the aquaculture industry and production, people who work for an advisory body or in the government apparatus, and people who have various other professional or hobby relationships with salmon. A total of 15 qualitative interviews are planned.

We would like to interview you because we believe that based on your position as ___, you will be able to contribute valuable knowledge that is relevant to the project.

What does it mean for you to participate?
If you choose to participate in the project, we will conduct a qualitative research interview with you. The interview will last for approximately one hour. We want to talk to you about your relationship with salmon, as a wild salmon and / or as a farm animal, and new technological opportunities in salmon production, more specifically gene editing tools such as CRISPR. We believe your experiences and perceptions about the technology; the salmon and farming will be able to give us important information about the project.

The project's motivation for using qualitative interviews is that we recognize the value of the experiences and opinions from people who are directly or indirectly involved in salmon farming.

We would like toto conduct the interview in person, but if the ongoing corona pandemic makes it difficult, video call is also an alternative. If there is a need for a follow-up interview, you will receive a new request which you can choose to accept or reject.

It is voluntary to participate
It is voluntary to participate in the project. If you choose to participate, you can withdraw your consent at any time and without giving any reason. All your personal information will then be deleted. It will not have any negative consequences for you if you do not want to participate or later choose to withdraw.

Your privacy - how we store and use your information
We will only use the information about you for the purposes we have described in this document. We treat the information confidentially and in accordance with privacy regulations. The following people will have access to the information: PhD candidate Torill Blix (GenØk / UiT) and PhD candidate Hannah Monsrud Sandvik (NTNU), Professor Bjørn Myskja (NTNU), Director Anne I. Myhr (GenØk), Professor Lotte Holm (University of Copenhagen).

The audio recordings will be transcribed, de-identified (personal information is removed and the interview participant will only be identified using a number key / code, further categories such as region instead of city and age ranges instead of specific age can be used) and thematically coded using NVivo or similar software . If you wish, you will have the opportunity to review quotes.
The data will be analyzed focusing on practices, values and perceptions of the salmon's moral status and the conditions for gene editing to be acceptable. This could be personally identifiable data with sensitive information. The data to be handled will consequently consist of audio files and text documents with transcribed interviews and analyzes of these. During the project period, these will be stored on a secure server at NTNU in a separate project-specific storage area protected with VPN and two-factor authentication. The storage solution will offer secure access to the data. External project participants will write access agreements.

The project will result in two doctoral dissertations, including 8-12 journal and book publications, as well as popular science articles / articles that summarize the findings of the project. The main emphasis in the analysis will be on content descriptions of perceptions of salmon, salmon production and new technological opportunities among various actors in salmon production. Your personal information will be de-identified in the dissertations and all publications. Where relevant, we would like to have the opportunity to say something about the type of position you have and the type of workplace you work at. This means that even if the interviews are de-identified by transcription and in dissertations and research articles, there is a possibility that you can be identified indirectly based on position and type of workplace.

What happens to your information when we end the research project?
The information is anonymized when the project is completed / the thesis′ is approved, which according to the plan is in the spring of 2023. The data will be stored long-term at NSD for later research. We will not leave the data openly available because some of the data material will be of such a nature that it will also be identifiable even after anonymization. It will therefore not be ethically justifiable to request consent for the data to be openly available in anonymized form.

Your rights
As long as you can be identified in the data material, you have the right to:
- access to which personal information is registered about you, and to receive a copy of the information,
- to have personal information about you corrected,
- to have personal information about you deleted, and
- to send a complaint to the Data Inspectorate about the processing of your personal data.

What entitles us to process personal information about you?
We process information about you based on your consent.

On behalf of NTNU, NSD - Norwegian Center for Research Data AS has assessed that the processing of personal data in this project is in accordance with the privacy regulations.

Where can I find out more?
If you have questions about the study, or want to exercise your rights, please contact:
Department of Philosophy and Religious Studies, NTNU by Bjørn Myskja by email bjorn.myskja@ntnu.no or telephone 73 59 09 51. Our privacy representative is Thomas Helgesen, email (thomas.helgesen@ntnu.no) or telephone: 93079038.

If you have questions related to NSD's assessment of the project, you can contact: NSD - Norwegian Center for Research Data AS by email (personverntjenester@nsd.no) or by phone 55 58 21 17.

Sincerely,

Bjørn K. Myskja — *Bjørn Kåre Myskja*

Anne Ingeborg Myhr — *Anne Ingeborg Myhr*

Hannah Monsrud Sandvik — *Hannah Monsrud Sandvik*

Torill Blix — *Torill Blix*

Samtykkeerklæring

I have received and understood information about the project Genome editing - a game-changer in salmon farming: Conditions for social and moral acceptance (CRISPRsalmon), and have had the opportunity to ask questions. I agree to:

- ☐ participate in interview

I agree that my information will be processed until the project is completed

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(Sign project participant, date)

Paper I

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REVIEW

REVIEWS IN Aquaculture

Genome editing on finfish: Current status and implications for sustainability

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[Correction added on 31 May 2021, after first online publication: Affiliation 2 has been added for the author Torill Bakkelund Blix and the city for affiliation 3 has been changed from Tromsø to Bergen.]

Abstract

Novel genome editing techniques allow for efficient and targeted improvement of aquaculture stock and might be a solution to solve challenges related to disease and environmental impacts. This review has retrieved the latest research on genome editing on aquacultured finfish species, exploring the technological progress and the scope. Genome editing has most often been used on Nile tilapia (*Oreochromis niloticus* Linnaeus), followed by Atlantic salmon (*Salmo salar* Linnaeus). More than half of the studies have focused on developing solutions for aquaculture challenges, while the rest can be characterized as basic research on fish genetics/physiology or technology development. Main traits researched are reproduction and development, growth, pigmentation, disease resistance, use of trans-GFP and study of the omega-3 metabolism, respectively. There is a certain correlation between the species identified and their commercial relevance, indicating the relevance of most studies for present challenges of aquaculture. Reviewing geographical origin of the research, China has been in the forefront (29 publications), followed by the United States (9) and Norway (7). The research seems not to be dependent on regulative conditions in the respective countries, but merely on the purpose and objectives for the use of genome editing technologies. Some technical barriers identified in the studies are presented together with solutions to overcome these-off-target effects, ancestral genome duplication and mosaicism in F0. One of the objectives for use is the contribution to a more sustainable aquaculture, where the most prominent issues are solutions that contribute to minimizing impact on biodiversity.

KEYWORDS
CRISPR, finfish aquaculture, genome editing, GMO regulations, off-target, sustainability

1 | INTRODUCTION

Aquaculture is the fastest growing food production industry on a world basis. In 2018, the share of aquaculture in total fish production was 46%.[1] Even though the production is growing, the negative effects of this industry often receive much attention. These challenges include diseases, escapees and ecological effects.[2] In Norway, the first-hand value of Atlantic salmon was 68 billion NOK in 2019,[3] and

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Norway accounts for over 50% of the world's total production of Atlantic salmon (*Salmo salar* Linnaeus).[4] Despite being highly economically viable and providing working opportunities and export revenues, salmon production is subject to controversies rooted in the challenges the industry faces related to environmental impacts and animal welfare, thus hindering sustainable development.[5,6]

The development of a more efficient aquaculture requires increased utilization of available genetic resources.[7] This includes use of valuable genetic material within selective breeding as for example marker-assisted breeding.[8] Genetic resources are also very useful for introduction, removal or single base exchange using genome editing (GE).[5,9,10] The use of GE demonstrates some promising possibilities for improvement of the aquaculture stocks,[11] with impacts for sustainable and efficient aquaculture.[5] The first approaches using genome editing included techniques as zinc finger nucleases (ZFN) and transcription activator-like endonucleases (TALEN). At present, the most novel method, the clustered regularly interspaced palindromic repeats (CRISPR) system, dominates. This system offers the possibilities of making small changes by fixing alleles and changing trait loci.[9] The CRISPR system is at present considered to be the most efficient, targeted and affordable genome editing technique.[12-14]

Further expansion of the aquaculture production, with the aim to meet future need for food and economic growth, requires contribution to sustainable development. Sustainable development was originally defined by the Brundtland Commission as the '[…] development that meets the needs of the present without compromising the ability of future generations to meet their own needs'.[15] In 2015, the UN set out the 17 common sustainable development goals (SDGs). These were based on the thoughts from the Brundtland Commission – and are common guidelines on how to achieve a sustainable world. The goals are integrated in each other, emphasizing that *everything depends on everything*, and provide a balance where the three dimensions of sustainable development, environmental, economic and social, co-exist.[16] According to Stockholm Resilience Center, food connects all the SDGs.[17] Aquaculture and fisheries are both crucial for future food security, and '[…] offer development pathways to contribute to a more prosperous, peaceful and equitable world'.[1] It is therefore also of crucial importance that new solutions like genome editing can be used in sustainable manners.

Here, we present findings from a systematic review on the current status of genome editing in aquacultured finfish species, hence extending previous reviews.[5,9,18,19,20,21,22] As published in the previous reviews,[5,9,22] there is still a high focus on reproductive traits, but this has recently been expanded to include genes related to other production traits such as disease resistance.

The geographical origin of the research and innovation activities using GE on aquaculture finfish has also been reviewed. In addition, we have compared the number of reports wherein genome editing is used on a specific fish species with the commercial relevance of the species in aquaculture. In the systematic review, several of the identified studies have included some discussion of technical barriers by genome editing including off-target effects, which is highlighted here with the potential solutions. These challenges are also of regulatory relevance and need to be addressed by concrete regulatory approaches.[23,24] Regulatory approaches and concerns have just been briefly discussed in previous studies.[7,21,25] Here, we describe the regulatory approaches in the main countries researching genome editing on aquacultured finfish, and whether the countries have included non-safety factors, as contribution to sustainability, socio-economic and ethical aspects, in assessment of genetically modified organisms (GMOs). Norway is one of the countries which have included non-safety criteria in the regulation of GMOs. Here, we briefly elaborate on how the Norwegian impact assessment regulation can be used for a sustainability assessment of genome edited aquacultured finfish species.

1.1 | Genome editing technologies

Since the discoveries of the DNA structure and function, further research has focused on the ability to modify gene sequences. Enzymes like polymerases, ligases and restriction endonucleases provide the ability to make changes through cutting and ligating, and the polymerase chain reaction (PCR) offers isolation of fragments. Repairing lethal DNA breaks is inherent in cells endogenous machinery. Thus, combining the possibility to both introduce breaks at the desired sequence and cellular self-repair is the foundation for GE.[26]

During the last 20 years, several new techniques for modifying DNA have emerged, both oligonucleotide-directed mutagenesis-based techniques (ODM) and nuclease-mediated site-specific mutagenesis techniques. In this review, we focus on targeted alterations of the fish genome and the site-specific nucleases (SSN), while also recognizing ODM-related activities such as RNA interference (RNAi). There are four categories of site-directed nucleases: meganucleases, ZFN, TALEN and CRISPR.[27]

ZFN is composed of modular DNA recognition proteins.[22] When associated with restriction enzyme FokI, the complex can be designed to recognize specific chromosomal sequences of 9–18 nucleotides, and at dimerization, the FokI enzyme can induce double-strand breaks (DSB).[26] Use of ZFN was established in 1996 and its use within research increased from 2003. The method was hampered by difficulties of design and validation of proteins for specificity in the complex. In addition, ZFN had low efficiency with very few mutations in F0 generation (parent generation), leading to low transmission to F1 generation (first filial generation). These challenges lead to a newer tool emerging in 2010/11, TALEN. As with ZNF, TALEN is using the restriction enzyme FokI and the cleavage requires dimerization. TALEN is, however, easier to design and validate than ZFN and recognizes fewer nucleotides, thus being more efficient than ZFN. The protein design, synthesis and validation are, however, still not efficient enough which hampers widespread use of this tool. All the site-directed nucleases use the organisms repair system to induce either site-specific mutations (insertion or deletion, *indels*) or insertions of new sequences.[27] The most recent technology, CRISPR/Cas nucleases emerged as late as 2012/13[26] and are molecular features of bacteria and archaea for recognition, thus

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protection against virus infection.[28] This system is RNA-mediated and performs sequence-specific detection and silencing of foreign nucleic acids. The CRISPR system is organized with the Cas proteins (CRISPR-associated proteins) encoded in operons and 'CRISPR arrays consisting of genome-targeting sequences (called spacers) interspaced with identical repeats'.[29] The repeats are short fragments from foreign nucleic acid that has entered the cell (e.g. by infection of viruses).[26] In the genome editing system, guide RNAs (gRNA) lead the CRISPR system to the target DNA sequence and cleave the target site by the nuclease. The first studies of the CRISPR/Cas system were performed in 1987, while the first publication on CRISPR system for GE was published in 2012.[29]

The nuclease-mediated site-directed techniques ZFN, TALEN and CRISPR induce a DSB at a specific site in DNA. This stimulates natural repair mechanisms. One repair mechanism is non-homologous end-joining (NHEJ), which induces random point mutations, inserting or deleting material (indels). Alternatively, if a donor DNA strand homologous to the sequences bordering the DBS is provided, a homologous directed repair (HDR) will happen. The type of donor determines the type of repair, insertion or replacement of a sequence within the DBS, correction of a base or deletion of a sequence.[9,27,30] The mutations lead to either knockout (KO) or knock-in (KI) of a gene or DNA sequence.

1.2 | Genome editing in aquacultured finfish

As well as being an important research tool, CRISPR could provide an efficient way to expedite genetic improvement of farmed animals. Aquatic animals are easy to work with compared to many terrestrial species due to high fertility rates, short generation time and external fertilization.[9] In 2015, Ye et al.[21] reviewed different fish breeding methods and pinpointed CRISPR system as promising for '[...] efficiency, precision and predictability [...]' in fish aquaculture. This was later followed up by Zhu and Ge[22] which published a study on recent advancements in genome editing on finfish, focusing on reproductive traits.[22] Other possibilities were later presented by Gotesman et al.[19] where genome editing and RNAi were pointed out as useful therapy tools for combating pathogens in aquaculture. A concomitant review by Elaswad and Dunham[18] described how different genetic and genomic tools for disease reduction in aquaculture could be achieved by the CRISPR/Cas system. They also highlight the possibility for knock-in (KI) procedures and to the benefits by the combination of genome editing and selective breeding.[18]

The increased speed of technology development within gen(ome) sequencing has aided the rapid development of genome editing technologies. Houston and Macqueen[20] reviewed the exploitation possibilities from sequencing and annotation of the Atlantic salmon genome. They build from Lien et al.[31] which was part of the Salmon Genome Project and had a special focus on the ecology, physiology and evolution of the salmon genome as well as highlighting further possibilities by genome editing. Wargelius[5] focused on sustainability issues related to Atlantic salmon production and other relevant solutions that genome editing may offer. Subsequently, Gratacap et al.[9] published a review on current technical possibilities that genome editing offers for aquaculture species globally. The latter publication listed 21 studies where genome editing was used (successfully) on different aquaculture species (including one oyster species) and categorized the solutions according to traits. To present the current and future status of use of genome editing on aquaculture finfish, we have performed a systematic literature review.

2 | METHOD

The methodological approach used for the systematic literature search is based on relevant items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[32]

2.1 | Search strategy

For identification of relevant scholarly articles, Google Scholar (GS) and Web of Science (WoS) were used as databases. Search strings included relevant terms as genome editing, aquaculture and aquaculture finfish species (Appendix 1). Only searches that had lower numbers of results (>700) were followed up to collect articles. During the search for articles on use of CRISPR in aquaculture fish species, both publications presenting experimental results and review articles were included. The WoS search included articles from 1995 to 2021 (as of 15.02.21) in order to include work using the ZFN or TALEN technologies. The GS search was restricted to get scholarly articles from the period 2015 to 2021 (as of 15.02.21) to narrow down the result list. Using GS, the retrieved articles were often duplicated since they were from different websites and often composed of newspaper/magazine articles or master theses, while WoS allowed for more precise search (e.g. no newspaper/magazine articles or master theses). Different search strings were also used (see Appendix 1). One search string contained a list of the major aquaculture finfish species given by FAO.[33] These 20 fish species made up 84,2% of total aquaculture production worldwide.[33] An updated list was published in May 2020[1] after the first searches were performed, but it did not contain any significant changes compared to the list of 2018.

The initial identification of articles was mostly based on titles. After identification, each of the abstracts was screened for exclusion records (see Appendix 1). Different exclusion criteria were made because the two databases yielded different types of output lists. This was followed by merging all retrieved scholarly articles having an experimental approach into one list, and any duplicates were removed.

2.2 | Grouping of data

The strategy for grouping the data was done inspired by Catacora-Vargas et al.[34] in order to identify the direction and location of the genome editing field associated with aquaculture finfish species. The

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review articles were used as supplements in the current work and were not analysed to the same detail as the experimental articles.

The data in the experimental articles were grouped after: species, objective of the study, trait, gene(s), type of genome editing results (NHEJ/HDR) and institutional affiliation of 1st author. The search for technical barriers in the articles was done through searching for relevant terms in all articles and then coding relevant paragraphs in NVivo 12.6.0 software, followed by analysis of the coding book.

3 | RESULTS

The GS searches dated 06.01.20 and 13.01.20 retrieved 295 and 673 results, with 25/27 and 48/38 relevant empirical/review articles, respectively. The GS search dated 15.02.21 retrieved 170 results with 9/2 relevant empirical/review articles. The searches were performed with different search terms. The two WoS searches dated 12.03.20 and 15.02.21 retrieved 73 and 25 results, with 30/8 and 16/0 relevant empirical/review articles, respectively (see Appendix 1). After comparing the lists with reports based on empirical work, the total number of empirical articles found was 56. Table 1 presents the resulting papers included in this review. The CRISPR/Cas system dominated the field of genome editing on aquacultured finfish (Figure 1). We found two scholarly publications using ZFN,[35,36] one study using TALEN[37] and two studies using both TALEN and CRISPR.[38,14] Use of the CRISPR technology was found in 52 publications. Publications using ZFN were not found after 2016 and TALEN not after 2018. The results from the search showed that publications on GE of aquaculture species emerged from 2012, however, cascade reading has also revealed one paper from 2011. This paper was not included in our study. The number of publications per year increased from 2012 to 2020 (Figure 1). The highest number of reports was published in 2020, and in addition, a publication peak was observed in 2016. The high number of reports using CRISPR compared to other methods supports the increasing interest in CRISPR, which may be due to availability, efficiency and affordability of the technology compared to the other two. This may also reflect the high number of publications in 2016 compared to 2015, considering the development of the CRISPR method from 2012 to 2013. As by the 15th of February 2021, four reports have already been published in 2021, indicating that the number of publications in 2021 might exceed 2020.

4 | DISCUSSION

4.1 | Species and traits

The search included the 20 most exploited aquaculture finfish species globally.[33] Table 1 lists the results according to species and area of interest, while Figure 2 shows the distribution of species. The two most studied species are Nile tilapia (*Oreochromis niloticus* Linnaeus) and Atlantic salmon. Today, the main traits that are selected for in aquaculture in the United States, Europe and China through breeding are growth, disease resistance, processing yields and product quality, reproductive traits, feed conversion efficiency, morphology and tolerance to environmental stressors.[7,87,88] It could therefore be expected that these traits would appear in the studies retrieved in this review. Reproduction (maturity/fecundity) and development were the most studied traits, found in this systematic review, see Figure 3. This also included sex determination and sterility. Then came growth, pigmentation, disease resistance, use of trans-GFP and omega-3 metabolism. The traits studied mirrors the most important traits in modern breeding, where, for example, omega-3 content in fish can be considered important for product quality for human consumption.

In Table 1, we have included categorization of what areas of interest the different papers indicate to have. Considering the CRISPR field of research to be quite young, we acknowledge that areas of interest in each study is/are focused on key issues such as maturity/fecundity – thus being overlapping. However, we have attempted to assign each study the field of interest we consider most prominent – for example being technology development or final product-oriented such as production of sterile fish for aquaculture.

4.2 | Geographical origin of genome editing research compared to major finfish producing countries

In our analysis of the literature, we investigated the institutional affiliation of the 1st author for each study to determine the geographical location of the research, see Figure 4. China is still on the top.[9,22] Others are the United States, Norway, UK, Japan, Egypt, Czech Republic, Republic of Korea, India, France and the Philippines. Some of the papers have been credited two countries because the 1st author had two institutional affiliations at the time of publication. China has produced most publications (29), followed by the United States (9) and Norway (7).

For countries with aquaculture production, the choice to consider genome editing as an approach may depend on the type of challenges the country/region faces, regulative conditions, knowledge about the species and wild relatives and consumers acceptance of GM/GE foods. Moreover, Wargelius[5] argued that a prerequisite for genome editing is that the species genome is fully sequenced and annotated. Considering these proposed criteria, we expect there to be some correlation between the species importance in present aquaculture production, for how long they have been produced, first selective breeding study (history of aquaculture), and to whether genome editing has been approached for this species.

According to FAO,[1] Asia is the major aquaculture producing region according to volume (88.69% of global production), and China is the largest country with a total of almost 58%. America produces 4.63%, Europe 3.75% and Africa 2.67%. It is evident that China as the most producing aquaculture country is also the one doing most research on the use of genome editing on aquacultured finfish.

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TABLE 1 Overview of genome editing in aquaculture finfish with respect to fish species, field of interest, specific trait and gene(s), additional remarks, genome editing system and institutional affiliation of 1st author. Abbreviations can be found listed alphabetically below the table. Genes *tyr2* and *slc45a2* when in parentheses are targeted for phenotypic visibility

Species	Interest	Trait	Target genes	Remarks	System	Institutional affiliation 1st author	Reference
Nile tilapia (*Oreochromis niloticus* Linnaeus)	Teleost genetics	Reproduction and development	*dmrt6*		CRISPR	China	Zhang et al.[39]
			aldh1a2, cyp26a1		CRISPR	China	Feng et al.[40]
			Rspo1		TALEN	China	Wu et al.[37]
			sf–1		CRISPR	China	Xie et al.[41]
			gsdf		CRISPR	China	Jiang et al.[42]
			wt1a, wt1b		CRISPR	China	Jiang et al.[43]
			eEF1A1b		CRISPR	China	Chen et al.[44]
			esr1, esr2a, esr2b		CRISPR	China	Yan et al.[45]
			amh homozygous, amhr2 homozygous, amh heterozygous, amhr2 heterozygous		CRISPR	China	Liu et al.[46]
			cyp11c1	Expression rescue	CRISPR	China	Zheng et al.[47]
			rln3a, rln3b		CRISPR	China	Yang et al.[48]
			igf3		CRISPR	China	Li et al.[49]
			tsp1a		CRISPR	China	Jie et al.[50]
			foxh1		CRISPR	China	Tao et al.[51]
	Aquaculture	Reproduction and development	*amh, amhbeta-y, amhy, amhrII*		CRISPR	China	Li et al.[52]
			piwil2		CRISPR	UK	Jin et al.[53]
	CRISPR as tool	Reproduction and development	*nanos2, nanos3, dmrt1, foxl2*		CRISPR	China	Li et al.[54]
			miRNA200a/200b/429a/+ssDNA, miRNA200a/200b, miRNA429a, miRNA125, vasa–3´UTR	HDR	CRISPR	China	Li et al.[55]
Mozambique tilapia (*Oreochromis mossambicus* Peters)	CRISPR as a tool	Reproduction and development	*OmbAct, OmEF1a, TU6*	Cell line	CRISPR	U.S.	Hamar & Kültz[56]
Atlantic salmon (*Salmo salar* Linnaeus)	Aquaculture	Pigmentation	*slc45a2, tyr*		CRISPR	Norway	Edvardsen et al.[57]
				HDR			Straume et al.[58]
		omega–3 metabolism	*Δ 6fads2-a, Δ 6fads2-b, Δ 6fads2-c, Δ 5fads (slc45a2)*		CRISPR	Norway	Datsomor et al.[59]
			elovl2 (slc45a2)		CRISPR	Norway	Datsomor et al.[60]

(Continues)

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TABLE 1 (Continued)

		Reproduction and development	*dnd* (*slc45a2*)		CRISPR	Norway	Wargelius et al.[25]
				Expression rescue	CRISPR	Norway/Czech Republic	Güralp et al.[61]
				HDR	CRISPR	Norway	Straume et al.[62]
Chinook salmon (*Oncorhynchus tshawytscha* Walbaum)	Aquaculture	Trans-GFP	*egfp*	Cell line	CRISPR	UK	Gratacap et al.[63]
	CRISPR as tool	Trans-GFP	*megfp*	Cell line	CRISPR	UK	Dehler et al.[64]
	Teleost genetics	Disease resistance	*stat2*	Cell line	CRISPR	UK	Dehler et al.[65]
Rainbow trout (*Oncorhynchus mykiss* Walbaum)	Teleost genetics	Reproduction and development	*sdY*		ZFN	France	Yano et al.[36]
		Growth	*IGFBP−2b1*, *IGFBP−2b2* (*tyr2*†)	Cell line	CRISPR	U.S.	Cleveland et al.[66]
					CRISPR	U.S.	Cleveland et al.[67†]
Various salmonid cell lines	CRISPR as a tool	Trans-GFP, pigmentation	*gfp*, *slc45a2*	Cell line	CRISPR	UK	Gratacap et al.[68]
Grass carp (*Ctenopharyngdon idella* Valenciennes)	Aquaculture	Disease resistance	*JAM-A*	Cell line	CRISPR	U.S.	Ma et al.[69]
Common carp (*Cyprinus carpio* Linnaeus)	Aquaculture	Growth	*TALEN: sp7, runx2, spp1a, mstn, CRISPR: sp7a, sp7b, mstnba, runx2, opga, bmp2ab*		CRISPR+TALEN	China	Zhong et al.[14]
	Teleost genetics	Pigmentation	*MCIR*		CRISPR	China	Mandal et al.[70]
	Aquaculture	Pigmentation	*ASIP*		CRISPR	China	Chen et al.[71]
Farmed carp (*Labeo rohita* Hamilton)	Aquaculture	Disease resistance	*TLR22*	HDR	CRISPR	India	Chakrapani et al.[72]
White crucian carp (*Carassius auratus civieri* Temminck & Schlegel)	Aquaculture	Pigmentation	*tyr*		CRISPR	China	Liu et al.[73]
Gibel carp (*Carassius gibelio* Bloch)	Teleost genetics	Reproduction and development	*Cgfoxl2a-B*, *Cgfoxl2b-A*, *Cgfoxl2b-B*		CRISPR	China	Gan et al.[74]
Loach (*Paramisgurnus dabryanus* de Thiersant)	CRISPR as tool	Pigmentation	*tyr*		CRISPR	China	Xu et al.[75]
Channel catfish (*Ictalurus punctatus* Rafinesque)	Aquaculture	Reproduction and development	*cgbb*		ZFN	China/U.S.	Qin et al.[35]
		Growth	*mstn*		CRISPR	U.S./Egypt	Khalil et al.[76]
		Disease resistance	*cath* (*Alligator mississippiensis*)	HDR, transgenic	CRISPR	U.S./Philippines	Simora et al.[77]

(Continues)

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TABLE 1 (Continued)

	CRISPR as tool	Disease resistance	*TICAM1*, *RBL*		CRISPR	U.S.	Elaswad et al.[78]
				HDR		U.S./Egypt	Elaswad et al.[79]
Southern catfish (*Silurus meridionali* Chen)	Teleost genetics	Pigmentation	*cyp26a1*		CRISPR	China	Li et al.[80]
Yellow catfish (*Pelteobagrus fulvidraco* Richardson)	Teleost genetics	Reproduction and development	*pfpdz1*		CRISPR	China	Dan et al.[81]
Sterlet (*Acipenser ruthenus* Linnaeus)	Aquaculture	Growth, trans-GFP	*ntl*, *egfp*		CRISPR+ TALEN	China	Chen et al.[38]
		Reproduction and development	*dnd1*		CRISPR	Czech Republic	Baloch et al.[12]
Tiger pufferfish (*Takifugu rubripes* Temminck & Schlegel), Red sea bream (*Pagrus major* Temminck & Schlegel)	Aquaculture	Growth	*mstn*		CRISPR	Japan	Kishimoto et al.[82] Kishimoto et al.[13]
Blunt snout sea bream (*Megalobrama amblycephala* Yih)	Aquaculture	Growth	*mstna*, *mstnb*		CRISPR	China	Sun et al.[83]
Olive flounder (*Paralichthys olivaceus* Temminck & Schlegel)	Aquaculture	Growth	*mstn*		CRISPR	Republic of Korea	Kim et al.[84]
		Growth, reproduction and development	*Myomaker*, *gsdf*		CRISPR	China	Wang et al.[85]
		Disease resistance	*PoMaf1*	Cell line	CRISPR	Republic of Korea	Kim et al.[86]

Abbreviations: *aldh1a2*, retinal dehydrogenase 1a2; *amh*, anti-Müllerian hormone; *ASIP*, agouti signalling protein; *bmp2ab*, bone morphogenetic protein 2; *cath*, cathelicidin; *cgbb*, gonadotropin subunit beta-2, LH gene β-subunit; *Cgfoxl*, Carassius gibelio forkhead box protein L2; CRISPR, clustered regulatory interspaced palindromic repeats; *cyp11c1*, cytochrome P450 11c1; *cyp26a1*, cytochrome P450 26A1; *dmrt1*, doublesex- and mab-3-related transcription factor 1; *dmrt6*, doublesex- and mab-3-related transcription factor 6; *dnd1*, dead end miRNA-mediated repression inhibitor 1; *eEF1A*, Eukaryotic elongation factor 1 alpha; *egfp*, enhanced green fluorescent protein; *elovl2*, fatty acyl elongase 2; *esr1*, *esr2a*, *esr2b*, oestrogen receptor gene 1, 2a and 2b; *fads2*, fatty acyl desaturases; *foxh1*, forkhead box gene h1; *foxl2*, forkhead box protein L2; *HDR*, homologous directed repair; *igf3*, insulin-like growth factor 3; *IGFBP-2b1/2*, insulin-like growth factor-binding protein 2b1/2; *itgb1b*, integrin β-1 b; *JAM-A*, Junctional adhesion molecule-A; *MCIR*, melanocortin 1 receptor; *megfp*, monomeric enhanced green fluorescent protein; *miRNA*, microRNA; non-coding sequence; *mstn*, myostatin; *OmbAct*, Oreochromis mossambicus Beta-Actin promoter; *OmEF1a*, Oreochromis mossambicus elongation factor 1 alpha; *opga*, osteoprotegerin; *nanos2*, *nanos3*, nanos-homologue 2 and 3; *ntl*, no tail; *pfpdz1*, Pelteobagrus fulvidraco PDZ domain-containing protein; *PoMaf1*, Paralichthys olivaceus MAF1; *RBL*, rhamnose binding lectin; *rln3a/b*, Relaxin3; *Rspo1*, furin-domain-containing peptide R-spondin 1; *runx2*, runt-related transcription factor 2; *sdY*, sexually dimorphic on the Y chromosome; *sp7*, specificity protein transcription factor 7; *spp1a*, secreted phosphoprotein 1; *slc45a2*, solute carrier family 45 member 2; *stat2*, signal transducer and activator 2; TALEN, transcription activator-like endonuclease; *TICAM1*, toll-like receptor adaptor molecule gene; *TLR22*, toll-like receptor 22; *tsp1a*, Thrombospondin 1a; *trans-gfp*, trans-green fluorescent protein, an isomer of GFP; *TU6*, Tilapia polymerase III promoter; *tyr*, tyrosinase; vasa-3′UTR, associated with germ cell development; *wt1a* and *wt1b*, Wilms tumour gene 1a and 1b; *ZFN*, zinc finger nucleases.

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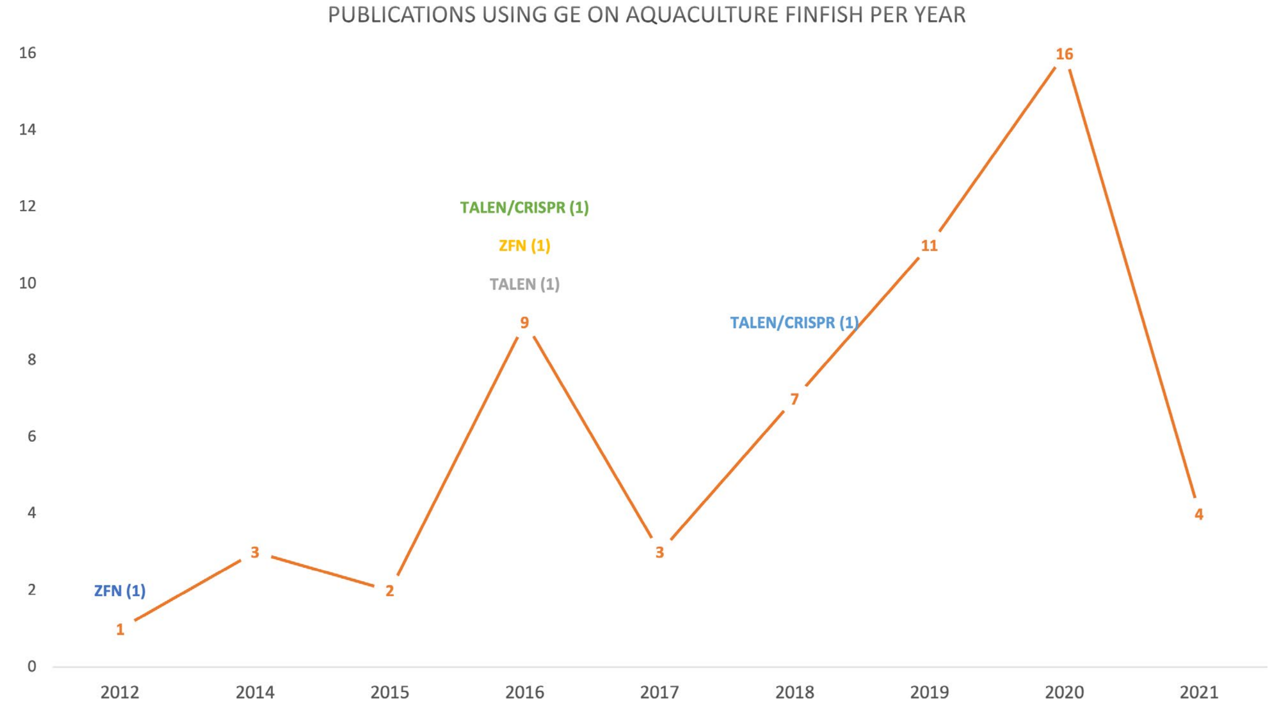

FIGURE 1 Number of articles using GE (genome editing) on aquaculture finfish species retrieved in systematic literature search published per year. Number of publications using other tools than the CRISPR (clustered regulatory interspaced palindromic repeats) system is highlighted with number of TALEN (transcription activator-like effector nuclease), TALEN and CRISPR, and ZFN (zinc finger nuclease)

Norway, the third most important country identified in our study, produces 1,65% of the total volume. Norway does however account for over 50% of the world's total production of Atlantic salmon.[4]

This history of aquaculture could also be compared to the species used in studies of genome editing to see whether there is a correlation between history of farming and the interest in novel tools like genome editing, see Table 2. Nile tilapia is the species which according to the review of Houston et al.[8] has been farmed for longest period, starting about 4000 year ago. The Nile tilapia genome was sequenced in 1998, and subsequent re-sequencing work has improved the coverage and quality of the annotations.[89] This species is also popular for use in research of fish physiology and endocrinology, with specific focus on sex determination and evolution,[55,90] as the results from this review also show. All the studies on this species have a first author associated with China, except one study from the UK (Table 1).

Various carp species show a very old history as aquaculture species, with first farming 2000–1000 years ago.[8] This is also the third most occurring species group in the articles retrieved in this review. All, except two articles on disease resistance in farmed carp (*Labeo rohita* Hamilton)[72] and grass carp (*Ctenopharyngdon idella* Valenciennes),[69] have 1st authors associated with China. Carp species are the most common freshwater aquaculture species in China.[99,100]

The second most studied species with regard to genome editing was through our retrieval, the Atlantic salmon. All these articles had their first author affiliated to a Norwegian institution, except one using Atlantic salmon cell line in the UK.[68] Norway is the third most dominate country in our findings. This might be because of the extensive research on salmon aquaculture in Norway, although showing a short history as a commercial fish species. Norwegian research focuses on breeding together with use of gene technology for marker-assisted breeding etc. facilitated by mapping and sequencing of the salmon genome. The Atlantic salmon has only been bred for about 50 years in Norway, yet it is already the species which globally has the most exploited traits for breeding programmes.[87] The genome of the Atlantic salmon was published as a bacterial artificial chromosome-based map first,[101] and later a high-quality whole genome of the Atlantic salmon was published by31 as part of the Salmon Genome Project.

4.3 | Technical challenges and off-target mutations by using CRISPR technology in finfish

The use of genome editing on finfish, either for commercial use or in research, brings technical challenges that should be considered. Some of these are off-target mutations and mosaicism in the F0 generation.[9]

4.3.1 | Off-target mutations

When genome editing leads to mutations in locations where it was not intended, this is called off-target mutation. These are the result

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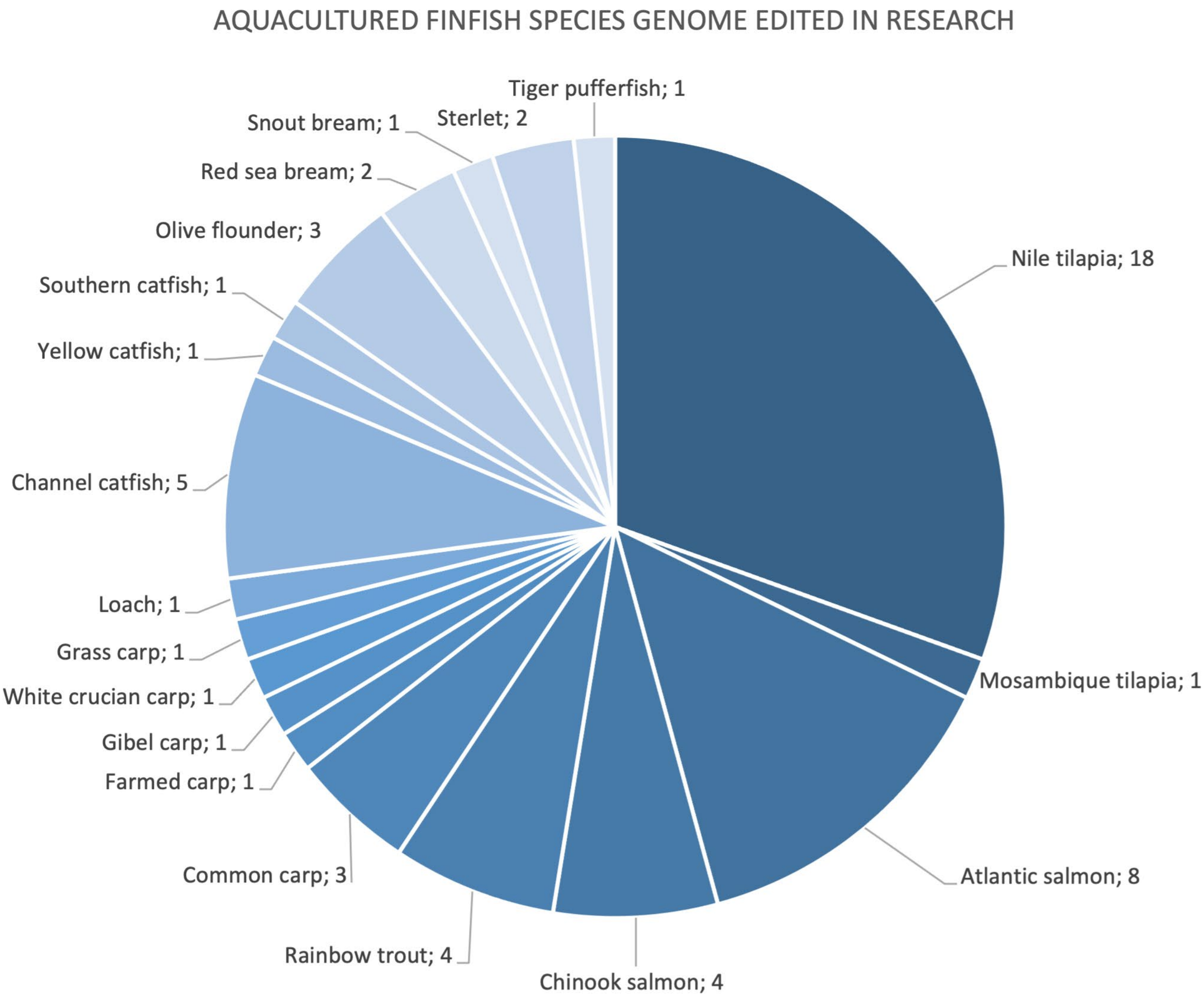

FIGURE 2 Distribution of species used for research on GE (genome editing) in publications found in systematic literature search. Species are sorted according to most used species (groups), and the numbers indicate the number of publications using the species

of the gRNA annealing to unintended or non-target areas of the genome, initiating mutations which might lead to unwanted and/or unknown effects on the organism as change in gene activity, gene silencing or gene knockout.[102] Off-target mutations are difficult to detect since the number and position of nucleotide changes are unknown.[23]

The first approach for avoiding off-target effects may be done by careful design of the gRNA by comparing the planned gRNA(s) to established genome assemblies, which has been done in several of the studies analysed in this review.[13,14,25,49,51,53,57,59,60,61,63,69,72,73,83] Some studies suspect embryo mortality[35,79] and embryo malformation followed by death[12] to be related to off-target effects. Simora et al.[77] experienced that increased mutation rate implied increased embryo mortality after inserting an alligator (*Alligator mississippiensis*) cathelicidin gene for pathogen resistance in Channel catfish (*Ictalurus punctatus* Rafinesque), suspecting this to be either off-target effects or pleiotropic effects. Elaswad et al.[79] argue that the specificity of the CRISPR/Cas9 depends on the protospacer adjacent motif (PAM) and the gRNA. They discuss that an off-target match with 5 mismatching nucleotides could still anneal to the gRNA as a target sequence and that this result could be minimized with better gRNA design. In addition, they suggest that the use of Cas9 nickase mutant with paired gRNAs would reduce the off-target effects. Elaswad et al.[79] do also point to the need for more research on the toxicity in relation to the concentration of gRNA injected into fish embryo, and to what extent this is related to off-target effects. One possible solution to this may be the use of short-life Cas9 variants, however, whether this approach reduces toxicity needs to be further investigated.[58] The second option for controlling off-target mutations is by routine rescreening of the genome for discovery of unintended mutations post-editing. This is, however, difficult since there is natural genetic variation in between strains and families which makes it difficult to find a good comparator to be able to identify potential off-target effects. Khalil et al.[76] report on not having examined the fish genome in edited fish for off-target mutations, only that '[...] no mutations were detected nearby and outside the target site'. Kishimoto et al.[13] found two mismatches for their small guiding RNAs (sgRNAs), however,

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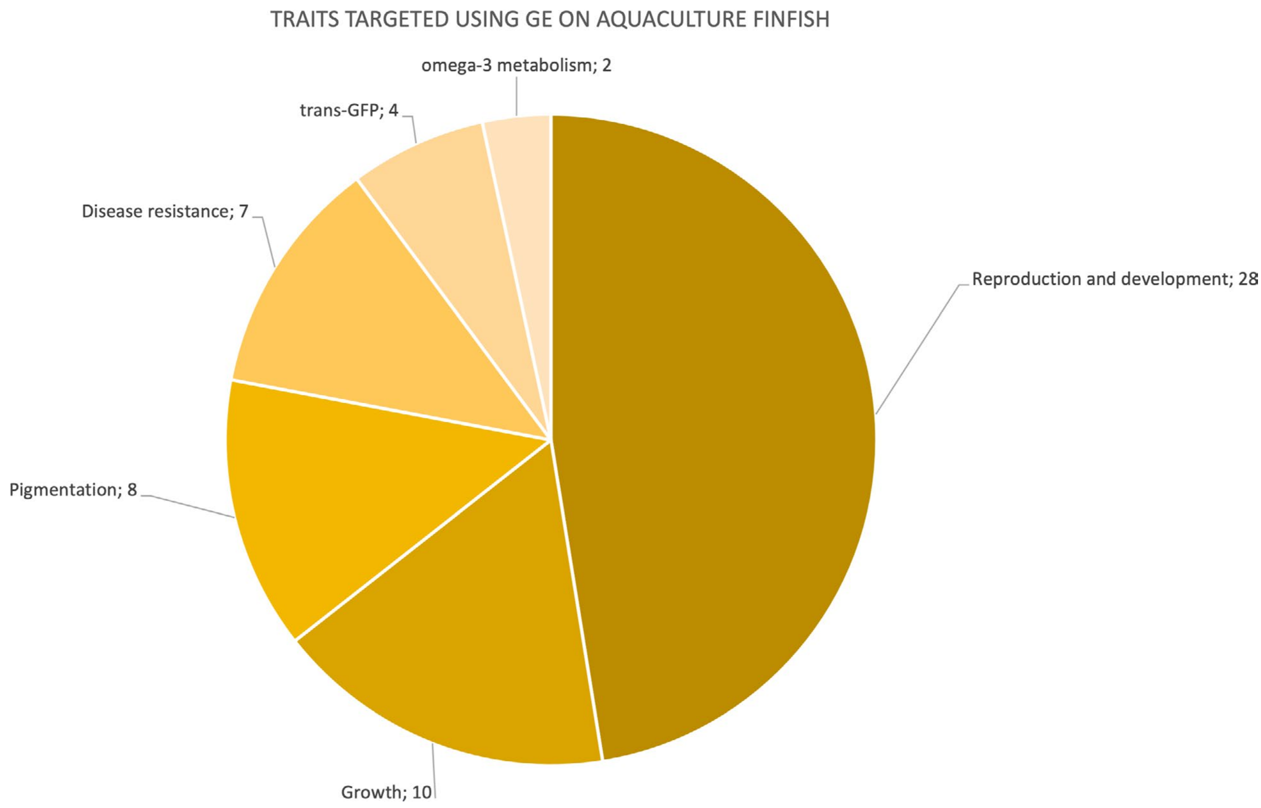

FIGURE 3 Distribution of traits studied using GE (genome editing) in articles retrieved in systematic literature search. Numbers are number of publications targeting the trait. Traits are reproduction and development (including sterility and sex determination), growth, pigmentation, disease resistance, use of trans-GFP (green fluorescent protein) and omega-3 metabolism

a screening post-editing showed that only one target sequence had mutation and thus excluded the possibility for off-target mutations in both F0 and F1 generation. Qin et al.[35] observed mutations within the open reading frame, but not at the ZFN targeted sequence position.

Considering the discussion from the papers identified in this review, there is a further need to identify the presence of off-target and other unintended effects. This may imply to use recent developments as next-generation sequencing and multi-omics approaches, as seen approached in Jin et al.[53] These methods need to be sensitive enough to distinguish between natural variation and mutations introduced by genome editing.

4.3.2 | Effect of ancestral whole-genome duplication

Another challenge relevant when discussing teleosts, and especially salmon, is ancestral whole-genome duplication (WGD) events and particularly the salmonid-specific 4th round (Ss4R). WGD is a duplication of the genome resulting in an extra set of all genes, followed by either sub-functionalization (duplicated gene remains unchanged and shares function of original gene), neofunctionalization (duplicated gene is assigned new function) or non-functionalization (duplicate loses function, e.g. as a pseudogene).[71,103] Because of several rounds of duplication events, different teleost species have different numbers of chromosomes and compositions and functions of paralogues,[45,65] and ploidy levels.[12] Ancestral WGD is a governing aspect when genome editing the teleost genome.[63] At the same time, different authors also emphasize that using genome editing is a convenient method for targeting and mutating genes in such duplicated genomes,[14,66] and Gan et al.[74] specifically used CRISPR/Cas9 to study the role of duplicated genes in Gibel carp (*Carassius gibelio* Bloch). If a group of species has different ploidy level, the one with lowest level should be used as model species for the rest of the group.[38] In the cases where two or more paralogues of a gene are identified, the function and sequence of the paralogues should be determined to consider whether these should be co-targeted or single-targeted, depending on the desired outcome of the mutation. Cleveland et al. emphasize the need for targeting and knocking out both gene duplicates for the protein IGFBP-2b to be able to disrupt the expression of the protein, since the paralogue of one gene may persist the function of the gene and eradicate the effect of the targeted mutation.[66] This was also seen in Datsomor et al.[60] discussing how paralogues can rescue the function of the gene knocked out and co-targeting may be needed to elucidate the function of a gene. In some cases, the duplicated genes might have evolved

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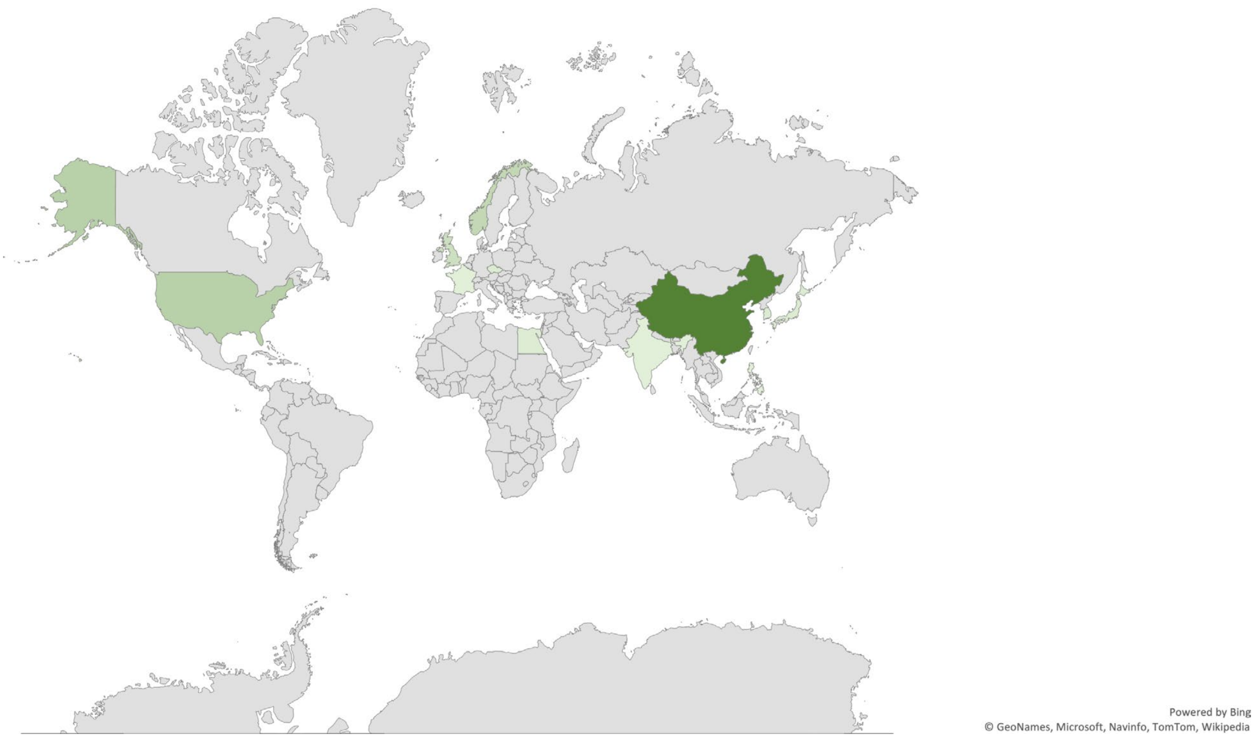

FIGURE 4 Countries involved in studies using genome editing on aquaculture finfish species, based on institutional affiliation(s) of 1st author of all studies retrieved. Darker to lighter colouring indicates the distribution of number of publications, from most to fewer

TABLE 2 Overviews of most used species according to production volume, time of first farming, first selective breeding, number of studies retrieved in this review using the species (56 in total) and genome-wide screening or sequencing of the latter

Production volume (FAO 2020)	Time of first farming (yr. ago) (Houston et al. 2020)	First selective breeding study (yr. ago) (Houston et al. 2020)	GE studies (#/56)	Genome-wide screen/sequencing reference
Grass carp	Nile tilapia (4000)	Rainbow trout (95)	Nile tilapia (18)	Kocher et al.[91]
Silver carp	Common carp (2000)	Atlantic salmon (50)	Atlantic salmon (8)	Lien et al.[31]
Nile tilapia	Grass carp (1000)	Nile tilapia (40)	Channel catfish (5)	Liu et al.[94]
Common carp	Silver carp (1000)	Common carp (40)	Chinook salmon (4)	Christensen et al.[92]
Bighead carp	Black carp (1000)	Labeo rohita (<40)	Rainbow trout (4)	Berthelot et al.[95]
Catla sp.	Bighead carp (1000)	Silver carp (<20)	Common carp (3)	Xu et al.[93]
Carassius sp.	Milkfish (500)	Grass carp (<20)	Olive flounder (3)	Shao et al.[128]
Osteichthyes	Labeo rohita (100)	Pangasius catfish (<20)	Sterlet (2)	Cheng et al.[97]
Atlantic salmon	Rainbow trout (100)	Wuchang bream (<20)	Red sea bream (2)	Shin et al.[98]
Labeo rohita	Atlantic salmon (50)		Grass carp (1)	Wang et al.[96]

Abbreviations: GE, genome editing; yr. ago, years ago.

new functions, as seen in Cleveland et al.[66] and Chen et al.[44] and then, depending on the desired outcome, single knockout is sufficient and will also reveal the function of each paralogue. Such an operation also depends on the relative difference between the sequences of the functionally different paralogues.[66] If possible, genes that occur only once in the genome can be chosen as a target for the editing to avoid disturbance, and this approach has been done by targeting *slc45a2* and *tyr* in Edvardsen et al.[57] and *dnd* in Wargelius et al.[25]

4.3.3 | Mosaicism

Mosaicism in the F0 generation relates to on what cell stage in the embryo that the editing occurs, as CRISPR system components such as the gRNAs might be degraded, depending on the developmental pace in different species.[104] The most convenient is editing at the one-cell stage. Of the articles retrieved in this review, several reported mosaicisms in their research animals.[12,47,49,51,53,57,59,61,71] Straume et al.[62] reported that mosaicism increased with higher

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injection volumes of oligonucleotide donor template. Cleveland et al.[66] emphasize that mosaicism is possible to overcome by generating a F1 generation. Edvardsen et al.[57] found that several individuals in F0 carried the same indel mutations, and a crossing to F1 would generate homozygous non-mosaic fish with the desired mutation. They express that such a result in the F1 generation is a quick process, even though species like salmon has a long generation time of 3–4 years.[57,62] Some studies used knockout of pigmentation as a way of selecting out mosaic individuals before analysis, as complete loss of pigmentation would show the F0 individual not to be a mosaic.[57,58,59,61,62,67] Edvardsen et al.[57] also found that fin clips can be used to identify the knockout phenotype of individuals as it followed the mosaicism to some degree.

4.4 | REGULATIVE FRAMEWORKS IN COUNTRIES DOING GENOME EDITING ON FINFISH – CRUCIAL FOR USE?

How to regulate genome edited organisms as plants and animals has during the recent years been discussed. Regulative issues concern both whether genome edited organisms should be regulated under present regulative frameworks for GMOs or if they should be exempted, and whether the regulation is according to product or process.[105,106] Compared to older GMOs, the newer genome edited organisms can be generated without use of transgene sequences.[105] This is a common topic of discussion, even though insertion of desired sequences is possible using HDR, as shown in four of the retrieved papers of this study.[55,58,72,78] Regulative concerns could affect the use of genome editing in applied research with the goal for commercial use.[9] It has been argued that GMO regulation may hamper research and innovation of genome edited organisms due to the excessive regulatory requirements placed on GMOs.[107]

Ishii and Araki[105] have presented an overview of the different regulative frameworks and made a distinction between those countries that regulate according to product or process. All countries identified in our review, except Norway and the Philippines, were represented in the list of Ishii and Araki. Of the countries identified in our studies, United States, Japan and Republic of Korea have implemented product-based regulations, while India, China and EU (France, Czech Republic) have implemented process-based regulations. Norway has a process-based regulation. UK was also identified as a European country during the research, but at present it is unsure what will be happening from the UK Brexit situation and as such the national legislations. The different ways of formulating the regulations affect whether it is the characteristics of the final organism and its direct effect, or the process and act of changing an organism through gene technology that accept or denies for cultivation and/or release. The latter triggering a specific regulation for GMOs, while in countries who have a product regulation the novel product is regulated under more general food/animal regulative framework. Ishii and Araki did not find any significant differences between countries having product or process-based regulation when it comes to commercial cultivation of GM crops.[105] From our studies, where China and Norway dominate, it seems like the type of regulation do not affect initiative for research, as suggested by Martin-Laffon et al.[107]

When it comes to the newer technologies available through genome editing on crops, Ishii and Araki[105] concluded that countries may be divided on how they will regulate genome edited plants. One example of this is Argentina who developed a new, own regulation for genome edited organisms that do not contain any transgenic DNA (Resolution No. 173/2015), in order to speed up the approval process.[105,108] A regulatory exemption was given for Aquabounty produced genome edited Nile tilapia. This fish is not considered a GMO and has been genome edited for increased filet quality and quantity and for more efficient growth.[109]

In the EU, a genome edited organism was decided by court decision to be a GMO, and so the EU regulation approval process does not divide between the different technologies. However, the European countries doing research on genome edited finfish, the Czech Republic and France has through the Directive (EU) 2015/412, amending Directive 2001/18/EC, a possibility to adopt measures restricting or prohibiting a group of GMOs defined by crop or trait. This can be based on grounds such as those related to socio-economic impacts, avoidance of GMO presence in other products, agricultural policy objectives or public policy (Article 26b[110]). Although this directive is specific on GMO crops, it can be assumed that the same possibilities will be relevant for genome modified and genome edited fish. Norway has through the EEA-agreement harmonized the EU Directive within national legislations.

Besides national regulation, there are also international treaties that regulate GMOs, as the Cartagena Protocol under the Convention on Biological Diversity (CBD). All countries identified and presented in this review, except the United States, have signed the Cartagena Protocol, which regulates import and export of GMOs.[105] Article 26 of this protocol emphasizes '[…] socio-economic considerations arising from the impact of living modified organisms on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities'.[111] This will favour taking biodiversity into consideration when evaluating new genome modified or edited organisms.

Country members of the EU and countries that have signed the Cartagena Protocol under the CBD have the possibility to consider broader aspects when evaluating genome edited and modified organisms. Such broader aspects can include the socio-economic significance of the production, potential ethical aspect (as animal welfare and consumer autonomy), and how the product contributes to sustainable development.[112] The type of regulative conditions regarding product or process in each country may therefore not be as important when it comes to future commercial use of genome editing,[105] the purpose and goals to be achieved by the genome editing may instead influence the decision and the acceptability of the technology. Ishii and Araki also call upon for more consistent policies, referring to the missing link between the regulation type,

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experience with GM crops and relation to the Cartagena Protocol within a country.

In 2018, the growth-enhanced transgenic AquAdvantage (Atlantic salmon) was approved for production in a land-based grow-out facility in Indiana, United States[113] In December 2020, a domestic pig genome edited for removal of galactosyltransferase alpha 1,3 (*GGTA1)* which enables synthesis of alpha-galactose on the cell surfaces was approved by FDA. The major aim was to reduce any hyperacute rejection of pig-to-human xenotransplants. Secondly, the porcine meat could meet food demands of people with allergic reactions caused by alpha-gal syndrome (AGS). As such, the GalSafe pig is intended to be used for both food and medical purposes.[114] These recent approvals of transgenic and GE animals, together with the recently approved GE Nile tilapia in Argentina, could indicate that future approvals of more GM/GE organisms in food production should be expected.

4.5 | CONTRIBUTION TO SUSTAINABLE DEVELOPMENT

Our review outline that some of the challenge's aquaculture is experiencing, like disease and genetic contamination in wild stocks, has possible solutions through genome editing. In Norwegian aquaculture, an expansion of the salmon farming industry requires transition to a more sustainable production. This final section will therefore discuss how the different solutions retrieved in this review can contribute to a more sustainable salmon production, based on how the contribution of genome edited organisms to sustainable development is evaluated under the Norwegian Gene Technology Act (GTA). The GTA is a unique regulation that requires, besides assessment of risk to the environment and health, consideration of the ethics, social utility and contribution to sustainable development of GMOs. This, in addition to the urgent need for innovation and new solutions in aquaculture, is reflected in the focus of the Norwegian studies retrieved in this review, where the aim is to generate a fish more appropriate for a sustainable aquaculture.[25,57,58,59,60,61,62] In support of the research on the germ cell free Atlantic salmon, other studies have looked at growth and maturation,[115] and other sterility candidate genes have later been explored.[116]

The legal document 'Regulations relating to impact assessment pursuant to the Gene Technology Act' describes what should be included in the assessment of sustainable development. This combines 15 control questions related to global impacts, ecological boundaries, human needs (distribution between generations and between rich and poor) and economic growth.[117] According to Rockström et al.[118] the main importance of sustainable development is for it to guide our activities to a safe operating space. This implies that we can produce and consume if it is with respect to the Earth system.[118]

The control questions regarding ecological boundaries and global effects on biodiversity should therefore be taken into wide consideration when evaluating genome edited organisms. All the control questions should also, according to the Norwegian Act, consider both the product and process, to ensure that sustainability is regarded throughout the whole production line/supply chain. The impact of aquaculture on nature environment is also to a large extent the driving force for proposing use of genome editing. However, solving ecological issues cannot have a negative impact on society and/or economy; therefore, all aspects must be evaluated.

The first control questions relevant for aquaculture finfish regarding global impacts and ecological boundaries ask whether the biological diversity is affected globally, whether the ecosystem way of function is affected and whether it will affect energy utilization, climate gases and pollution. Here, the research on reproduction and development is important. Sterile fish will not be able to reproduce with wild stocks after escape, and hence, the impact on environment will be reduced. In Norway, the issue with escaped fish is highly urgent. Güralp et al.[61] have recently published a method using a combination of genetic sterility and rescue, which may allow large scale production of sterile salmon.[61] A sterile fish will not only aid this issue, but it would also be considered a prerequisite for using genome edited fish in ocean pen production. Here, we do, however, want to emphasize the need for more research on how such a sterile salmon would impact wild relatives and surrounding biodiversity when it escapes.[119] Disease resistance could aid any aquaculture sector globally, and it would aid both the economic efficiency of the production, but also animal welfare and the impact on wild stocks, thus both biodiversity and responsible productions aspects of sustainability. Increased welfare is, alongside with sustainability, assumed an important argument for application of genome editing in aquaculture, especially in a country like Norway where ethical responsibility is implemented in the Act.[120] In addition, the Norwegian Animal Welfare Act states that all animals, including fish, have intrinsic value independent of their utility for humans, and shall be treated well and protected from unnecessary pain and strain.[121] Any implementation of genome editing in aquaculture has to consider this and elaborate how animal welfare should be considered for the species in question.

Secondly, the control questions include questions on the distribution of benefits and risks between generations and rich and poor. Anticipation of both the potential beneficial and adverse consequences of using genome editing in aquaculture is difficult because there is no former use to refer and learn from. Regarding GMOs, the standard implication is often that even though we remove an issue, for example disease resistance, some other issue will follow, as for example a new pathogen implying that one need to consider a longer timeframe when assessing potential impacts.

Another important aspect regarding future generations is the preservation of the wild salmon stocks in Norway. Norway holds approximately 25% of the total world population of Atlantic salmon, which has encouraged the preservation of this species.[122,123] In this context, a sterile genome edited fish is not only a solution, but should be a prerequisite for use. Other considerations to be made are whether genome editing allows for intensification or maintenance of the aquaculture production volume. If the former, is that representing a threat or benefit for the opportunities of future generations?

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The knowledge earned from studies of genome editing in one species can be used, albeit to a certain degree, in another. The research performed can therefore be useful for other countries with other aquaculture related challenges, including poorer countries with less resources to conduct this kind of expensive research on their own. This transfer of knowledge depends on transparency of the process and the product.

Finally, the control questions are summed up in questions on how the ecological impacts and distribution between generations and rich/poor affect the economic growth. These questions are not directly related to the solutions proposed, but an economic analysis that is outside the scope of this review. We will, however, go briefly through how economic traits could contribute to sustainability.

Pigmentation can be an economic trait, as seen for common carp in various colours, but also a tool in development and use of genome editing like CRISPR/Cas9. Regarded to be a commercial and ornamental trait, this modification will affect goals related to economy through social interest as for example aesthetic value. Both pigmentation and the use of trans-GFP have been applicated in studies aiming at developing CRISPR or TALEN as tools for aquaculture. The sustainability contribution of this use of genome editing will therefore depend on the knowledge generated from the activities. It could, however, also have importance for biosafety as the lacking pigmentation can be used to identify escaped genome edited fish.

In studies looking into growth, eight out of ten studies had aquaculture as main focus (Table 1). Increasing growth for increased production efficiency is valuable for reducing feed costs, but could have implications for welfare, as seen with bone defects after *sp7* and *mstn* KO in common carp.[13,14] In Norwegian salmon production, growth has for long been an important trait in breeding efforts, and here the process is regarded a success. Increased growth can therefore not be regarded as priority in the development of a sustainable production in Norway.

Omega-3 is especially relevant in Norwegian aquaculture, as sufficient amounts of omega-3 fatty acids sustain health benefits for both fish and humans.[59] As described by Datsomor et al.[59,60] LC-PUFAs in the feed is an important contribution to omega-3 synthesis in the salmon. This could lead to less need for live feed and/or fish oil in the feed, which would be of economic and ecological benefit.[124] Efforts within the genome editing field have also been aimed to generate omega-3 producing plants for use in fish feed.[125] This could be an alternative for approaching the issue more directly, alternatively in combination.

Lastly, we want to express the necessity for modifications, additions and changes to be made for the sustainability guidelines to be adapted for evaluation of GE and GM animals, and aquaculture finfish species more specifically, as seen for herbicide tolerant crops in Catacora-Vargas[126] and by the Norwegian Biotechnology Advisory Board.[127] We find it necessary not only to adapt the questions to evaluation of living GM/GE animals, but also to specify the core ideas and evaluation questions. It does, however, give a brief idea of the complexity of addressing genome editing solutions as sustainable because they might (contribute to) solve environmental issues. More study is needed on how to evaluate sustainability in relation to genome editingo fish, in addition to (experimental) study of the effect of genome edited finfish on environment, economy and society.

5 | CONCLUSION

We have found that the main traits researched are reproduction and development, growth, pigmentation, disease resistance, use of trans-GFP and study of the omega-3 metabolism. Compared with previous reviews, we find that there are other genes targeted in more recent studies. Reproduction is still the most targeted trait, but there is also an increase in other traits such as disease resistance, pigmentation and omega 3-metabolism. The knowledge from these studies is relevant both in aquaculture and in more basic research areas like physiology and genetics, and hence not only related to food production animals. At the same time, knowledge about the reproductive cycle, sterility and development is important in the development of an efficient and secure breeding process. Several of the studies mention technical issues such as off-target mutations, the effect of whole-genome duplications and mosaicism. There is a need of more research on the mechanisms and effects by off-target mutations. One identified solution is careful design of the gRNA. Methods used for identification of off-target effects require further elaboration, and these need to be sensitive enough to distinguish between natural variation and mutations introduced by genome editing. There is also a need for more studies on the phenotypic effects of genome editing, and this includes welfare and behavioural studies. Most of the studies retrieved in this review neither discuss implications for welfare, nor ethical considerations related to the activity of modifying the DNA of living organisms.

There is correlation between major producing countries of aquaculture finfish products and the geographical location of research on genome editing in aquaculture finfish. We also saw that a majority (26) of the studies (56) state utilization in aquaculture is the main objective of their research. This implies that there might be interest in the given countries for considering genome editing as a possible solution to aquaculture challenges and development. We have mentioned several regulative factors, like the product/process question, the Cartagena Protocol, the EU Directive 2015/412 amending Directive 2001/18/EC and the Norwegian Gene Technology Act. All these concerns and treaties affect how a country can, and have to, regulate genome modified and/or edited organisms. Based on the research activities in different countries, it seems the question of acceptability is more related to the purpose of the organism and product rather than the regulative conditions in the given country.

All the solutions found in this review can contribute to sustainability in each their own way. We emphasize the importance of

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prioritizing environmental sustainability in this regard. Biodiversity is of crucial importance to any food production system, also aquaculture. Its preservation should therefore be of main interest to both breeders, policy-makers and consumers. Evaluating the effect of a GMO on sustainability is required by law in Norway, and description for assessment has been developed for this specific term. These are, however, not fit for a thorough evaluation of live animals and should be revisited.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX 1

TABLE A1 Systematic literature search details for finding literature on genome editing research in aquacultured finfish species

Search strings	Excluded in search	Database	Date	Period	Results (#)	Selected articles	Review	Empirical
crispr/cas9 farmed atlantic salmon	News articles, ethics-related, conventional breeding, agricultural species, PhD theses, Master theses, basic research fish health, GE feed, patents	Google Scholar	06.01.20	2015–2020	295	52	27	25
salmon aquaculture crispr	Crustaceans, miRNA, interference RNA, sex determination, embryonal development	Google Scholar	13.01.20	2015–2020	673	85	38	47
"TALEN" OR"zinc finger nuclease" OR"CRISPR" OR"CRISPR/ Cas9" AND "Grass carp" OR"silver carp" OR"common carp" OR"nile tilapia" OR"bighead carp" OR"carassius" OR"catla" OR"Osteichthyes" OR"atlantic salmon" OR"*roho labeo*" OR"pangasius" OR"milkfish" OR"tilapia" OR"clarias" OR"Wuchang bream" OR"rainbow trout" OR"cyprinidae" OR"black carp" OR"snakehead" OR"*ctenopharyngodon idellus*" OR"*hypophtalmichthys molitrix*" OR"*cyprinus carpio*" OR"*Oreochromis niloticus*" OR"*hypophthalmichthys nobilis*" OR"*catla calta*" OR"*salmo salar*" OR"*labeo rohita*" OR"*chanos chanos*" OR"*Megalobrama amblycephala*" OR"*Oncorhynchus mykiss*" OR"*mylopharyngodon piceus*" OR"*channa argus*"	News articles, ethics-related, conventional breeding, agricultural species, PhD theses, Master thesis, basic research fish health, GE feed, patents	Google Scholar	15.02.21	2020–2021	170	11	2	9
	Research in human physiology, microbiology, environmental DNA, zebrafish, medaka, virology	Web of Science	12.03.20 15.02.21	1995–2020 2020–2021	73 25	38 16	8 0	30 16

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Paper II

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A sustainability assessment framework for genome-edited salmon

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ABSTRACT

In this paper we present a suggestion for a sustainability assessment framework using genome editing of salmon as a case study. The salmon farming industry is facing several challenges hindering sustainable production. Genome editing has entered as a tool that can improve selective breeding and feed ingredients in aquaculture, hence providing solutions such as resistance to salmon lice and other pathogens, and sterility reducing interbreeding with wild, threatened stocks. As a goal for aquaculture is that its practices and products contribute to sustainability, the use of genome editing needs to be assessed with regards to sustainability, too. In our work, we draw on three sources of information; strategy and policy documents published by governmental offices and industry organizations; relevant GMO regulations and operationalization reports; and qualitative empirical data from 19 semi-structured interviews with Norwegian key stakeholders, and four semi-structured citizen groups. The findings from our analyses are discussed in relation to a Wedding cake-model for sustainability developed at the Stockholm Resilience Centre based on the UN SDGs and the three pillars of sustainability: biosphere, society, and economy. Analysis of document and interview data shows three main findings, one within each of the sustainability pillars. First, we identified that the biosphere pillar, including protection of the environment and the wild salmon, is the major sustainability issue and therefore important for the assessment of sustainability in the aquaculture industry and for the potential introduction of genome-edited salmon. Second, in the pillar for society the preservation of cultural and natural resources should be included, and in the Norwegian context this includes preserving the Sámi culture reliance on the wild salmon stocks. Third, in the economy pillar animal welfare needs to be included both for efficiency and ethical responsibility in farming. With some adoption to local and national conditions and the fish species in question, the same framework can be used for sustainability assessment of genome edited finfish in general.

1. Introduction

Aquaculture is becoming the primary source of seafood and has the potential to be crucial in the transition to a sustainable global food system (BFA, 2021). One of the important species groups are Salmonids (Golden et al., 2021; FAO, 2022), and Norway is at present the largest producer of Atlantic salmon (*Salmo salar*, from here just salmon) globally (Iversen et al., 2020). Globally, production of salmon covers 32.6% of the total production of marine and coastal farmed fish (FAO, 2022). The Norwegian production of salmon is a young industry with an attributed blooming potential. The production increased from an input of 98,000,000 individual salmon in 1995 to 388,000,000 individuals in 2020 (Directorate of Fisheries, 2022, *Input 1994–2021)*. The value on slaughtered fish reached 64 billion NOK (approximately 6,3 billion Euros) in 2020 (Directorate of Fisheries, 2022, *Sales 1994–2020*). The industry employs 7103 people (2020) in Norway, mainly in the three northernmost counties and on the west coast, which is double the number of employees compared to 2010 (Directorate of Fisheries, 2022, *Number of Employees 1994–2020*). It is considered one of the most important and valuable industries in Norway, both for national value creation and for local communities (Ministry of Trade, Industry and Fisheries, 2021). The salmon farming industry is facing several challenges hindering sustainable production, such as salmon lice (*Salmonis lepoptheiruis)*, viral and bacterial diseases affecting welfare of the farmed fish (Sommerset et al., 2022). According to the annual fish health report by the Norwegian Veterinary Institute (Sommerset et al., 2022), 54 million farmed salmon died before slaughter in 2020, and they state that it is crucial to focus more on the welfare of the fish, rather than the size

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of the produced biomass. The most severe environmental impact the industry has is related to escapees and spread of disease from farmed to wild salmon. The farmed salmon standing biomass exceeds the wild stocks several hundred times over (Grefsrud et al., 2022), which leads to an immense selection pressure for bacterial, viral and parasitic pathogens such as infectious salmon anemia virus and the salmon lice (Thorstad et al., 2021), pathogens affecting welfare and that will spread to the environment and the wild stocks. In 2021, 61,133 salmon escaped (Directorate of Fisheries, 2022, *Losses in production*) and some of these may also have negative ecological and genetic effects on wild stocks (Bradbury et al., 2020), which can lead to a decline in wild populations (Thorstad et al., 2021). The wild salmon in Norway is at present considered to be an endangered species, and entered the Red List as *near threatened* in 2021 (Hesthagen et al., 2021). Another challenge is feed, although the use of fish meal and oil has been reduced, the industry is still dependent om imported feed resources as soy, showing the importance to find alternative feed ingredients of superior quality from local sources (Albrektsen et al., 2022).

Genome editing has entered as a tool that can increase efficiency and improve selective breeding. It holds promises for novel approaches to vaccine development, for increased nutritional content in aquaculture feed, and for removal and/or introduction of traits in aquaculture breeds such as salmon. Genome editing is a term covering several gene technologies which are used to change genetic sequences in vivo or in vitro of an organism or cell. Currently, CRISPR/Cas (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated proteins) (Doudna and Charpentier, 2014) is the most used genome editing technology in research on aquaculture finfish (Blix et al., 2021), for thorough overviews of application in finfish please see e.g., Blix et al. (2021), Hallerman (2021), Okoli et al. (2021), Yang et al. (2021). Genome editing technologies are separated from older techniques such as genetic modification (GM) because genome editing techniques are faster and more targeted (Okoli et al., 2021). Different changes can be introduced in the genome as for example site-specific mutations with non-homologous end-joining (NHEJ) termed Site Directed Nucleases (SDN)-1. Alternatively, a shorter or longer stretch of genetic sequence from the same species or from other species can be inserted together with the SDN, and the breaking of the DNA leads to insertion of short or long genetic sequence (SDN-2 or SDN-3) through homologous-directed repair (HDR) (EFSA, 2012).

Salmon is one of the most researched aquaculture species in this field, with Norway as head of the research. Currently, the traits which are most researched using genome editing for this species is sterility and pigmentation (Blix et al., 2021). Sterility entails a solution to one of the environmental concerns as sterile salmon cannot breed with wild populations after it escapes (Blix et al., 2021; Güralp et al., 2020; Wargelius, 2019), while pigmentation is relevant as a tool for research. Other solutions currently under research are salmon lice resistance (Nofima, 2021b), CMS (cardiomyopathy syndrome) resistance which is the main mortality factor in Norwegian industry today (Nofima, 2021a; Sommerset et al., 2022), and enhanced omega-3 production (Datsomor et al., 2019a, 2019b; Jin et al., 2020). Thus, genome editing holds promises for improving the sustainability and efficiency of the salmon industry by reducing impact on wild stocks and improve animal welfare.

The novelty of genome editing has triggered discussions on the adequacy of present GM legislation and if there is need to label products based on genome editing as GM (Turnbull et al., 2021). As our case study is genome editing of salmon aquaculture in Norway we adhere to a Norwegian legal context. Norway has its own Gene Technology Act of 1993 (GTA; Ministry of Climate and Environment, 2005a), follows EU GMO directives through the EEA agreement, and are signatories to the international Cartagena Protocol, a legal context where a genome-edited salmon is considered to be a new type of genetical modification. The GTA includes requirements for ethical justifiability, social utility and contribution to sustainability. The assessments of these three criteria are currently under discussion (Antonsen and Dassler, 2021). In addition, even though genome-edited organisms might be (partly) excluded from GMO legislation in Norway (Bratlie et al., 2019), as it has been on a case-by-case basis in the U.S. and Argentina, it can still be argued that genome-edited organisms should be assessed for their contribution to sustainability considering the disruptive nature of the technology (Myskja and Myhr, 2020). From this follows the question, what is needed for a sufficient sustainability assessment of genome-edited fish?

Recent years it has been a focus both by governmental agencies and the industry on the need to enhance sustainability in aquaculture practices and products. As with increased focus, the objectives and indicators for the assessment of sustainability is evolving. At the same time, it is recognized that indicators and assessment frameworks need to be contextual and dependent on the type of aquaculture system applied, as well reflect the aquacultured species as there are huge variations between them regarding their requirements for handling, feed and environmental conditions. Our analysis use farmed genome-edited salmon in Norwegian ocean facilities as a case with the purpose of elaborating a sustainability assessment framework for genome-edited salmon in aquaculture using three sources of information; strategy and policy documents published by governmental offices and industry organizations; relevant GMO regulations and operationalization reports; and qualitative empirical data from 19 semi-structured interviews with Norwegian key stakeholders, and four semi-structured citizen groups. This work contributes to the growing knowledge on stakeholder and citizens views on genome-editing in food production (Bearth et al., 2022; Busch et al., 2022; Kantar., 2020; van der Berg et al., 2021), and to the more general discussion of how to operationalise sustainability in aquaculture.

2. Theory: Sustainability in policy and regulation

Sustainability has been set as a prerequisite for the future life of humans on Earth. It is a term which is widely used, defined, and understood, and it is a leading aim for the development of “green” industries. Historically, the term sustainable development is of young age, but the wider meaning of sustainable development, resource use and human interaction with Earth systems can be found centuries back (Du Pisani, 2006). In the 1980-ties the World Commission on Environment and Development was asked to formulate a “global agenda for change” (Brundtland et al., 1987). The resulting report *Our common future* aimed at defining common ideas about how to combine development with environmental conservation. The definition of sustainable development was defined as development that “[…] meets the needs of the present without compromising the ability of future generations to meet their own needs” (Brundtland et al., 1987, chapter 1). After this, sustainable development was successively operationalized in common goals. In 2015, the UN redefined the Millennium Goals into 17 sustainable development goals (SDGs) in *Transforming our World: the 2030 Agenda for Sustainable Development*, from here just Agenda 2030 (UN, 2015). These are based on the thoughts of Brundtland et al. (1987), and are developed for all countries with the aim to have common guidelines on how to achieve a sustainable earth. There are 17 people-centred goals with 169 targets in total. The SDGs are integrated in each other, emphasizing that *everything depends on everything*, and balance the three dimensions of sustainable development: environmental, economic, and social (UN, 2015).

2.1. Sustainability in aquaculture policy

Several initiatives and organizations (e.g., FAO, 2022; BFA, 2021) have pointed to seafood as crucial for future sustainable food production. Globally, the Ocean Panel has stated that seafood should be increased by a six-fold by 2050 (Stuchtey et al., 2020). This expansion requires reducing negative environmental impacts from aquaculture and enhancing sustainability in the industry. The Norwegian Government recently published a strategy where they call for «[…] increased growth in the aquaculture industry within sustainable limits" (Ministry of Trade, Industry and Fisheries, 2021 p. 8, our translation). Even though the strategy opens with referring to the Ocean Panel calling for the necessity of more seafood to feed a growing population, the arguments for producing salmon along the Norwegian coast are related to national value-creation, sustaining local coastal communities, and creating an income for the common good (Ministry of Trade, Industry and Fisheries, 2021). According to the strategy, environmental sustainability should be of main priority. The Government also look to the EU taxonomy for sustainable economic activities (EU Technical Expert Group on Sustainable Finance, 2020), even though criteria for aquaculture are not yet included in this taxonomy. This is one way of ensuring the aquaculture to move in a more sustainable direction, by directing the capital to "green" investments only (Ministry of Trade, Industry and Fisheries, 2021).

Within aquaculture there has been developed several voluntary certification schemes, which represent a different way to measure how sustainable the industry is (Amundsen and Osmundsen, 2018). Within this system, aquaculture producers need to comply with given indicators and standards adopted to different aquaculture systems to achieve a certification. For salmon aquaculture there are eight major certification systems, these includes the Aquaculture Stewardship Council and Global Aquaculture Alliance. Amundsen and Osmundsen (2018) analysed indicators of the eight major certification schemes. They identified 28 topics, grouped in relation to governance (50% of the indicators), environment (47%), economics (3%) and culture (1%). Within these certification schemes the focus is on the environment (including fish health and welfare), while social implications are almost not included (Amundsen and Osmundsen, 2018; Amundsen, 2022).

2.2. Regulation and sustainability assessments of GMOs

Internationally, living modified organisms (LMO) (equivalent with genetically modified organisms (GMOs) and genome-edited organisms), are regulated by the Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity (CBD). The main objective of the CPB is to protect biological diversity against LMOs as these organisms are moved between countries. The CPB has 173 signatories, including Norway and excluding the U.S. and China (CBD, 2020), which are the top 3 countries researching genome editing of aquaculture finfish (Blix et al., 2021). The CPB defines biosafety as a term which ensures safe use of modern biotechnology considering human health and the environment, while at the same time recognizing the possibilities that such technologies might offer (CBD, 2000). According to Article 16 Risk Management of the CPB, all signatories shall create mechanisms and systems for identifying LMOs or traits in such organisms that might "[…] have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health […]" (CBD, 2000, Article 16). However, at present no specific guidelines for risk assessment of LMO fish has been implemented. The CPB includes socio-economic considerations in Article 26 specifying that this is related to the impacts on "[…] the conservation and sustainable use of biological diversity, especially regarding the value of biological diversity to indigenous and local communities" (CBD, 2000, Article 26). A dedicated expert committee has been assigned to work on socio-economic consideration, and they have suggested a specific guideline for the process (CBD, 2019), but not developed any indicators or specific guidelines for any LMOs.

In the EU, genome-edited organisms are currently regulated as GMOs after a Court decision in 2018 (Court of Justice of the European Union, 2018). Therefore, an application of commercial use of a genome-edited organisms must follow a risk assessment in accordance with the regulation, a process that for which the European Food Safety Authority (EFSA) has developed guidance's. EU regulation of GMOs, here included GM plants, microorganisms and animals, covers contained use, deliberate release, labelling and food safety. In addition, member countries can restrict or prohibit the production of GMOs instate (Directive EU 2015/412), based on e.g., concerns for socio-economic consequences in line with non-safety related concerns. Recently the commission has initiated work on a new legislation for plants produced by certain genomic techniques (EC, 2021) where sustainability assessment is suggested to be included.

At the national level, different GMO regulatory frameworks have been developed (Ishii and Araki, 2017). In Norway, the production and use of GMOs is regulated by the Norwegian Gene Technology Act of 1993 (GTA) (Ministry of Climate and Environment, 2005a). Currently, genome-edited organisms are treated as GMOs as in the EU. Norway was one of the first countries adopting non-safety factors and has the longest experience with sustainability assessment of GMOs. The GTA requires that the GMO, besides being safe for health and environment, must contribute to sustainable development, is ethically justifiable and has societal utility – three non-safety criteria in the Act. The procedure for the evaluation of the non-safety criteria is given in appendix 4 to the *Regulations on impact assessments of the Gene Technology Act* (Ministry of Climate and Environment, 2005). The Norwegian Biotechnology Advisory Board (NBAB) is responsible for advising the Ministry on new applications regarding the non-safety criteria. For this task, they have operationalized the guidelines for assessments of contribution to sustainability and for societal utility (NBAB, 2009, 2014, 2018). After a request from the Norwegian Environment Agency, an expert group has suggested how the ethics criterion can be operationalized (Forsberg et al., 2019).

The framework for sustainability assessment (NBAB, 2009) includes control questions within five core ideas, and for each core idea there are correlated control questions regarding both production and use of the GMO. The framework has been used as a starting point for the assessment of different plants and adapted to their characteristics and cultivation context (NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016). At present there are no guidelines for the assessment of GM animals (Blix and Myhr, 2021; Blix et al., 2021). In Table 1 from Blix and Myhr (2021) core ideas from the official NBAB framework have been combined with main topics elaborated for a diversity of GM plants. The table indicates that these guidelines can be used as a starting point for the assessment of GM animals, however, animal welfare needs to be further elaborated as these guidelines only covers impacts on animal welfare by consumption of feed based on GM plants.

2.3. Stakeholder and citizen involvement in sustainability assessment

In addition to normative data found in policy documents, it is important to look to descriptive, empirical data from engagement with relevant stakeholders, including citizens, to develop a sustainability assessment framework. This aims to ground the assessment in practices and values. Such an inclusion will provide that diverse needs and concern will be identified, and such interaction can improve adaptation, and flexibility in translating local practices into frameworks or sustainability schemes (Amundsen, 2022). Inclusion of stakeholders and citizens will also provide crucial information in assessment about local environmental conditions as well as local and traditional knowledge (Olesen et al., 2011). As described by Myrvold et al. (2019), the salmon is also of great cultural and social importance in Norway, and it is an important ecological and cultural species in Sámi culture (Sámi Parliament, 2021), the indigenous people in Norway. In addition, earlier research on the production of farmed salmon in Norway and Tasmania by Lien (2015) shows that people working close to the salmon in the farming industry expresses care towards and about the farmed salmon, hence providing information that can explain or supplement written materials. Such participatory approach is also of high value for the assessment of novel technologies as they will provide an appreciation of ethical and social values, as illustrated by Bremer et al. (2015) in their study on GM salmon.

Table 1
From Blix and Myhr (2021): Combination of NBAB sustainability guideline document (2009) with relevant topics developed for specific GM crops (NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016).

Original guideline document (NBAB, 2009)	Operationalization of guidelines: Report on plants adapted to salmon (NBAB, 2011, 2014, Catacora-Vargas, 2014, Gillund and Myhr, 2016).	
	Pillars	Topics
Global effects *Ecological limits* *Basic human needs* *Distribution between generations* *Distribution between rich and poor* *(For all core ideas: Do these effects differ between production and use?)*	Ecology and environment	The genetically modified organism Interaction between the GM and the environment Gene flow to wild relatives Preservation of biological diversity in ocean and rivers Resistance in salmon to diseases and parasites Comparison with control salmon (farmed) Safety of human health and the environment over time
	Economy and society	The right to sufficient, safe and healthy food Animal welfare* Living conditions and profitability for fish farmers and coastal communities in short and long terms Biodiversity and genetic resources for food and aquaculture Independent risk assessment Freedom to choose a different aquaculture system in the future

* *Animal welfare is a topic in NBAB (2014) and Catagoras-Vargas (2014). However, this was regarding the use of the evaluated plant for animal feed, not for a GM animal.*

3. Materials and methods

The making of the framework for assessment of sustainability is based on policy documents, strategies, and reports from governmental offices, agencies and interest groups related to either aquaculture, food production or natural resource management. In addition, the topics and control questions necessary for the assessment has been rooted in empirical data from semi-structured interviews with 19 stakeholders and four citizen groups. Interviews with stakeholders and citizen directly or indirectly involved with the salmon farming was carried out as this was considered to provide important knowledge and to give a fuller understanding of how sustainability is perceived, supplementing the documents. For developing the framework, we used the previous GM crop reports as a starting point (NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016). In addition, we hypothesized that it would be useful to base the framework on the UN SDGs and the Wedding Cake-rearrangement of the SDGs (Rockström and Sukhdev, 2016). Aspects, topics, or relevant questions identified in the documents, reports and in the interviews were therefore systematized according to whether they answered to either the biosphere, society, or economy. Accordingly, analysis of the documents and interviews also included identifying ways of defining sustainability to be used for the elaboration of the structure of the framework.

3.1. Policy documents

Documents were used to supplement the empirical interview data (Bowen, 2009), and were identified both before, during and after the interviews were conducted. The documents were chosen based on two necessities: First to identify how sustainability is understood and operationalized generally, both on a global and national (Norway) basis. Second, we needed documents that could be used to identify how sustainability could be operationalized in aquaculture. On global level we chose documents connected to the UN and the EU published after the UN SDGs in Agenda 2030 (UN, 2015). On national level we chose documents produced by the Norwegian government, the Sámi Parliament, and a strategy made by an industry federation for the aquaculture sector. The 9 final documents were not systematically selected and therefore some relevant documents may have been left out.

The authors read each their documents, searching for text describing *a) sustainability,* and b) *sustainability in aquaculture* in order to identify what is conceived as requirements for a system or product to be sustainable. The text sampled was used to elaborate an appropriate structure of the framework, and to elaborate topics to be used for assessing contribution to sustainable development. For the latter, the topics to include in the assessment were written in the form of (control) questions, as this is more appropriate for the assessment format and has previously been done in the GM crop reports (NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016). This was performed by condensation of statements in the documents which could be related to sustainability. The condensed statements were merged across the different documents and re-stated into control questions. Only those documents mentioning animal welfare has been used to inform the discussion on how to relate animal welfare to sustainability.

3.2. Qualitative interviews

3.2.1. Study design

The study was conducted as part of a larger study on genome editing of farmed salmon (project CRISPRsalmon: https://www.ntnu.edu/crispr-salmon). Semi-structured, explorative interviews were conducted with stakeholders of the salmon farming industry and with citizens in group interviews. Involving stakeholders and citizens in the research ensures that it is inclusive and rooted in real-world experiences of what it means to produce and consume farmed salmon, and to protect farmed and wild salmon, and nature. Initially, focus group interviews were planned to generate data via interaction between group members. However, because of the COVID-19 pandemic, all interviews had to be performed on video link. The main flow of communication during interviews took place between moderators and participants one by one, reinforced using the "raise-hand"-function in the video meeting software. We therefore have analysed and refer to the focus group interviews as group interviews.

The interviews covered both personal, ethical and sustainability aspects of farming salmon, but here we present only findings more specifically related to sustainability. While the strategy documents present normative views on what the industry should look like from the point of view of policymakers and stakeholders, the qualitative interviews present the more personal views of individuals involved in or with the industry, including citizens. It follows, that the views may align with, but should not be seen as representative of stakeholder or citizen views (Brinkmann and Kvale, 2014 p. 127).

3.2.2. Interview guide

The semi-structured interview guide (Brinkmann and Kvale, 2014) was developed pre- and in parallel to the recruitment process. The questions planned were systemized according to three themes: animal welfare and relations to salmon, genome editing, and sustainability. The guide is briefly described in the following list:

- For the theme animal welfare and relations to salmon we asked what the participants thought of the salmon as an animal and about their personal relationship towards it, what fish welfare is and how to practice it, and differences between fish and terrestrial animals with regards to this.
- For the theme genome editing we asked about advantages and/or disadvantages by genome editing of the farmed salmon, differences between the genome editing technology and older modification

techniques, differences between conventional breeding and using genome editing, intrinsic value and whether using genome editing is wrong, and whether they would buy genome-edited salmon if available.

- For the theme sustainability we asked participants to elaborate what sustainable development is (to them), whether a genome-edited salmon could contribute to sustainability, and whether they could see connections between sustainability and animal welfare.

3.2.3. Recruitment of participants

For *the stakeholder interviews* relevant stakeholder groups were identified during the search for relevant documents. The main stakeholder groups identified can be viewed in Table 2. Before recruiting participants, the Norwegian Centre for Research Data (NSD) was notified about the sampling and use of personal information (NSD reference number 707095).

From the analysis of the strategy documents relevant candidates within each stakeholder group were identified as individuals holding leading positions. Further, snowball recruitment was performed using declining and accepting candidates, members of the research group, and fellow advisors as mediators. The invitation letter included information about the project and a declaration of consent to be signed by the participants. Date for interview were agreed over email. In total, 38 candidates were invited to participate, whereof 19 responded positively and participated in an interview, from here *participants*. The remaining 19 candidates declined or did not respond to the invitation, or responded positively first, but then didn't respond to further communication. Reasons given for declining were lack of time, self-perceived bias or fear of their personal opinions being leaked to the public. Table 2 shows the number of participants in stakeholders and citizen groups. The number of participants per stakeholder group varies because groups which work directly with salmon on a daily basis and groups whose information could not be found by a literature search were prioritized.

For the *group interviews with citizens*, identification and recruitment of participants was performed by IPSOS, a world-wide marketing analysis company well experienced in marked surveys. For three of the groups, IPSOS recruited individuals from the Norwegian population, from different regions in Norway, and with maximum variation according to age (18–80), genders and ethnicity. A fourth group was recruited with people who only have Sámi background in addition to the criteria above. Recruitment was done from IPSOS panel of people already consent to participate in focus groups, and by "snowballing" from declining candidates using them as mediators. In addition, targeted Facebook ads and search in relevant Facebook groups with and without "snowballing" was done. Relevant and accepting participants were informed about the practical details concerning the focus group per email. Extra recruitment was done for all groups, to ensure adequate participation in case of insufficient turnout. Selected participants signed a standard declaration about GDPR and how data is stored generated by IPSOS. Final selection of participants was made on the day of interviews and aimed to ensure relevant spread of geographical location, age, and gender. Participants not selected for participation were compensated with the same 500 NOK (approximately 49 Euro) voucher as participants that were selected.

Table 2
Interview groups with reference code used in Table 4 and number of interviews per group.

Groups	Reference code	Number of interviews
Scientists using genome editing in fish	SGE	4
Trade union participants	TUR	2
Salmon farmers	SAF	4
Fish health workers	FHW	3
NGO-participants	NGO	2
Advisory body participant	ABR	1
Sami resource management	SRM	1
Wild salmon management	WSM	2
Citizen group Norwegian	CGN	3×6
Citizen group Sámi Norwegian	CGS	1×6

For citizen groups the number shows number of groups × number of participants per group.

3.2.4. Interviews

The individual interviews with stakeholders were held in digital videocalls over Zoom or Teams by researchers from the CRISPRsalmon project and lasted for about an hour. All stakeholder participants had to sign a declaration of consent as part of the NSD requirements for data sampling through qualitative interviews. The interviews were audio recorded and transcribed verbatim by project researchers.

The group interviews with citizens were conducted in digital videocalls using the same interview guide as in stakeholder interviews. Researchers from the CRISPRsalmon project were moderators, and representants from IPSOS participated as practical helpers and notetakers. Interviews were audio recorded. During the interviews IPSOS took extensive notes and modified them afterwards drawing on the audio records to provide more detailed transcripts. Group interview transcripts were not verbatim.

3.2.5. Analysis

The aim of the present analysis was to generate suggestions for control questions to applicants for commercial use of genome-edited salmon, which could be used directly in a sustainability assessment framework, as previously done (NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016). The interviews were coded post transcription using the terms concern/criteria, looking for all kinds of statements which could be read as either a concern regarding or criteria for accepting the use of genome editing on farmed salmon. The coded segments where then analysed by grouping the statements into the following themes *technology-related concerns, sustainability, societal utility* and *other concerns*. We performed a condensation of meaning (Brinkmann and Kvale, 2014, p. 231–235) by grouping statements related to sustainability which were similar across stakeholder and group interviews. Subsequently, the statements were merged and re-stated into control questions ((Brinkmann and Kvale, 2014), p. 231–235). Statements made by participants would take different forms, and they were not always made directly regarding sustainability. However, during analysis of meaning, statements were found to be linked to sustainability challenges. An example of this is animal welfare which could be considered part of an ethics assessment. However, based on our previous work (Blix and Myhr, 2021), this was considered a topic under sustainable economy as it is important for improving production efficiency and ensuring having a responsible production and consumption (UN SDG 12). Some of the concerns/criteria identified in the analysis were not appropriate to re-state into single control questions, but rather had the form of general topics of sustainability.

3.3. Making a sustainability assessment framework

In the aftermath of the Agenda 2030, Rockström and Sukhdev (2016) remodelled the SDGs in a model that aims to explain how the goals are linked to food production. Fig. 1 shows this model. The intention by the model is to re-shape approaches and considerations of sustainability, and it implies other requirements for institutions and industries who wants to assess how their work contributes to the goals and prohibits the "shopping" of the most relevant/suitable goals. According to Rockström and Sukhdev (2016) this model represents a new way of viewing the three pillars of sustainability. The "wedding cake" is an iconic figure developed at Stockholm Resilience Centre by Folke (Folke et al., 2016). The model represent how economy serves society in order for society to evolve "[…] within the safe operating space of the planet" (Rockström and Sukhdev, 2016). This model is used as the foundation of the framework generated here. In the framework, the control questions generated by analysis of interviews and documents are merged with

Fig. 1. Restructured model for the UN SDGs by Rockström and Sukhdev (2016), illustration by Azote for Stockholm Resilience Centre (CC BY 4.0).

control questions from pre-existing frameworks (Ministry of Climate and Environment, 2005; NBAB, 2011, 2014; Catacora-Vargas, 2014; Gillund and Myhr, 2016). Finally, the control questions were structured into respective *topics* and the topics were placed within the more appropriate level of sustainability – biosphere, society or economy, based on the SDGs within each level (see Table 4).

4. Results and discussion

In this section we will present and discuss how the results from the analyses of interviews and documents can inform a sustainability assessment framework for genome-edited salmon. Considering the scope of the data reviewed for the making of the framework, this paper will not

Table 3
Documents retrieved in document search.

Document groups	Document title	Reference	Target groups	Related documents (examples)**
Global sustainability	*Transforming our World: the 2030 Agenda for Sustainable Development*	UN (2015)	All countries and stakeholders	*Millennium Development Goals* (UN 2000), *Universal Declaration of Human rights* (UN 1948)**
	Farm to Fork Strategy (here: FF)	(EC, 2020)	European policy makers and citizens	European Green Deal (2019)**, Agenda 2030 (UN, 2015)
	Building Blue Food Futures for People and the Planet (2021) (here: BFA)	Stockholm Resilience Centre, Stanford University, EAT (BFA, 2021)	Policy makers globally	*Agenda 2030 (*UN, 2015*), Food security and nutrition: building a global narrative towards 2030* (HPLP 2030)**
	Mission Starfish 2030: Restore Our Oceans and Waters (here: Starfish)	European Commission et al. (European Commission et al., 2020)	European policy makers and citizens	IPCC Special Report on the Ocean and Cryosphere in a Changing Climate (2019)**, Global assessment report on biodiversity and ecosystem services of the IPBES (2019)**, European Green Deal (2019)**, *Agenda 2030* (UN, 2015)
National government on sustainability	*Food, Humans and Environment. Norwegian actions plan for sustainable food systems in developmental politics and foreign affairs for 2019–2023**(here: FHE)*	The Norwegian Governmental Ministries (2019)	National authorities	*Agenda 2030* (UN, 2015), Paris agreement (2015)**, Sendai Framework for Disaster Risk Reduction (2015)**
	*Sámi Parliament Statement on Area and Environment: Meahcci – a foundation for identity, culture and birgejupmi**(here: SPA)*	Sámi Parliament (2016)	All Sámi Parliament activities	Sámi Parliament Statement on Area and Environment (2009)**, CBD (2000), The Norwegian Nature Diversity Act (Ministry of Climate and Environment, 2009), The Finnmark Act (2020)**
National government on aquaculture/ salmon	*An Ocean of Possibilities – The Governments Aquaculture Strategy**(here: NGAS)*	Ministry of Trade, Industry and Fisheries (2021)	National, local and regional authorities, research, management and the aquaculture industry.	*Transformations for A Stable Oceans Economy* (Stuchtey et al. 2020), Agenda 2030 (UN, 2015), The Granavolden Platform (2019)**
	*Sámi Parliament Statement on Salmon: Diddi, lousjuolgi, goadjin ja duovvi**(here: SPS)*	Sámi Parliament (2021)	All Sámi Parliament activities regarding cases of wild salmon management/farming of salmon	Agenda 2030 (UN, 2015), CBD (2000), ILO Convention no. 169 (1989)**, International Covenant on Civil and Political Rights (UN 1966)**
Aquaculture industry strategy	*Roadmap for Aquaculture (here: NI)*	The Federation of Norwegian Industries (NI, 2017)	All member companies	Agenda 2030 (UN, 2015)

* Document is only available in Norwegian, our translation of title, original title in reference list.
** Documents are not used in text elsewhere and therefore not listed in references.

go into detail on all topics and control questions. This section first presents and briefly discusses the most important results from documents and interviews, respectively. Then we discuss the two topics which stands out: indigenous and local people's knowledge and rights and animal welfare. Quotations presented here from the documents published in only Norwegian, and from the interviews except two, are based our translation.

4.1. Policy documents

The documents identified and analysed are presented in Table 3. The documents have been grouped into different categories based on the target group they approach; on what level they have been produced, and according to the level of the challenges they discuss. Based on these criteria the following groups and documents were identified:

- Global sustainability documents are the UN Agenda 2030 (UN, 2015), The Farm to Fork Strategy (EC, 2020), the EU document Mission Starfish 2030: Restore Our Oceans and Waters (European Commission et al., 2020), and the Blue Food Assessment Summary Report (BFA, 2021). These global documents are used to identify how sustainability is, and could be, understood and operationalized on a global level, with specific emphasis on food production systems, oceans and marine food.
- National documents are Food, Humans and Environment, Norwegian actions plan for sustainable food systems in developmental politics and foreign affairs for 2019–2023 (The Norwegian Governmental Ministries, 2019), and Sámi Parliament Statement on Area and Environment: Meahcci – a foundation for identity, culture and birgejupmi [*to get by*] (Sámi Parliament, 2016). These documents contribute to the description of how Norway perceive and operationalise sustainability on the governmental level, including the Sámi resource management.
- Governmental documents on aquaculture/salmon, here represented by the Norwegian government in An Ocean of Possibilities – The Governments Aquaculture Strategy by Ministry of Trade, Industry and Fisheries (2021), and the Sámi Parliament Statement on Salmon: Diddi, lousjuolgi, goadjin ja duovvi (Sámi Parliament, 2021). The former focuses on aquaculture production of fish, while the latter on wild fish management, and are therefore not comparable, but both gives information about Norwegian salmon management.
- Finally, we have identified a strategy, amongst many, on aquaculture, written by one of the trade unions, The Federation of Norwegian Industries Roadmap for Aquaculture (NI, 2017).

Since the nationality in question is Norway, we acknowledge that if the framework was to be based on the politics and food production system of another country, other documents would be analysed, and other challenges approached. However, considering the inclusion of global documents, the framework will be relevant for other countries and a diverse system of animal protein production as well. This list of documents in Table 3 is not exhaustive, but the documents identified all contribute to describe how to define and operationalise sustainable development from a global to a local level.

4.1.1. Different routes to sustainability in aquaculture

Table 3 lists related documents for each identified document, showing both the context and the background for the documents. The Agenda 2030 (UN, 2015) have been cited in all identified documents, except the Sámi Parliament Strategy on Area (Sámi Parliament, 2016). We find that this clearly indicate the usefulness of utilizing the 17 UN SDGs for assessment of sustainability. The SDGs have been criticized for setting goals that are not possible to measure, for being too ambiguous, having a complicated language, being non-binding, and for top-prioritizing everything leaving nothing to be main priority (Swain, 2018). When implementing the SDGs into an organisation, an industry, a supply chain or the like, it is inevitable that there is a need for focusing the sustainability work, making some internal goals within the common goal of achieving a more sustainable Earth. When the global "receipt" for sustainable development is 17 goals within different areas - ocean, health, equality, production, and consumption and so on, it is also inevitable that industries solve the task of operationalising sustainability by picking those goals that they feel connected to and responsible for. The problem with such a solution is the risk of using a fragmented approach and overlooking systemic effects. Can an industry really ensure sustainable development in their production if they only focus on equality or production and consumption? This is identified in some of the other documents. The Federation of Norwegian Industries document *Roadmap for Aquaculture* (NI, 2017) states that important SDGs for their work are 2: Zero hunger, 3: Good health and well-being, 13: Climate action, and 14: Life below water (NI, 2017). Similarly, the Sámi Parliament Statement on Salmon (Sámi Parliament, 2021) emphasizes SDG 14, and the Norwegian Sustainability Strategy on Food, Humans and Environment (The Norwegian Governmental Ministries, 2019) states that SDG 2 is most important. The latter document does, however, emphasize that food production involves all SDGs, which has also been stated earlier by Rockström and Sukhdev (2016) as "[…] food connects all the SDGs".

A possible consequence of this prioritization of SDGs is a narrow assessment of how a sustainable system should be build. If this is transferred to an assessment framework it can give a skewed impression of what sustainability is. This has also been shown by Amundsen (2022) with regards to aquaculture certification standards where the pitfall is that «[…] the map becomes the terrain» if the assessment is reduced to a rigid scheme (Amundsen, 2022). Amundsen summarizes related papers looking at the certification system for aquaculture and finds that certification standards is most valuable when acknowledging that these are simplifications of reality (Amundsen, 2022). The assessment of genome-edited salmon is different from certification standards as it is performed pre-commercialization, however, the principle of checking boxes in a scheme is similar. A framework should not be a rigid list of questions, nor focus on singular SDGs. Having a clear, fundamental idea about what sustainable development is could be helpful in order to maintain some flexibility in the assessment process.

4.1.2. Documents propose biosphere-focused framework

Considering the discussion above, we have analysed the documents for how they define sustainability, directly or indirectly. The analysis shows the importance of the biosphere in most documents, albeit the strategies might differ.

The Food, Humans and Environment document focuses on how food is relevant for several of the SDGs and brings food production into global affairs and developmental politics, thus inserting Norway in the larger picture and as part of the global food systems. The three pillars are here said to be equally important (The Norwegian Governmental Ministries, 2019). The same focus is found in the Farm to Fork strategy, which also includes reflection on the COVID-19 pandemic showing connections between "[…] our health, ecosystems, supply chains, consumption patterns and planetary boundaries". The strategy points out that increasing sustainability will enforce resilience, and that solutions should be nature-based, technological, digital and space-based (EC, 2020).

The need to, and importance of, preserving and protecting ecosystems in resource management, protecting wild salmon and protecting ecosystem services is raised by the Farm to Fork strategy (EC, 2020), the EU Mission Starfish (European Commission et al., 2020), the Governments Aquaculture Strategy (Ministry of Trade, Industry and Fisheries, 2021), the action plan Food, Humans and Environment (The Norwegian Governmental Ministries, 2019), and the Agenda 2030 (UN, 2015). The EU Mission Starfish emphasizes the importance of protecting the oceans and water systems as these are fundamental for life on Earth. Ecosystem services and resources in and of water, and the possibilities of "[…]

leisure, well-being and growing economy is presented as reasons for protection and restoring. At the same time, the strategy report also mentions the importance of oceans and waters for "[…] culture, identity and sense of belonging", and that the value of the oceans and waters as common good overrules their economic value. The benefits are first and foremost related to ecology, society and culture (European Commission et al., 2020). The Sámi Parliament Statement on Area reflect on how to understand sustainability by stating that traditional use of resources has been "[…] in balance with available resources and area" (our translation), with respect to future generations possibilities and at the same time be able to utilize nature to make a living and feed yourself, to get by, the concept of *birgejupmi* (Sámi Parliament, 2016). This indicates that a focus on environment and society should be of main prioritation, and that preserving nature for future use is important. We find the similar descriptions in the Sámi Parliament Statement on Salmon (Sámi Parliament, 2021).

The BFA policyreport ((BFA, 2021) suggested that focusing on blue foods "[…] could also reduce the pressure on Earths resources" even though "Simply increasing the production of blue foods is not the solution […]". The topic resilience in food production systems is emphasised by the Farm to Fork Strategy (EC, 2020), the action plan Food, Humans and Environment (The Norwegian Governmental Ministries, 2019) and the BFA policy strategy . This is related to topics ecology and resilience in food production systems and respective control questions in Table 4. However, are the SDGs possible to combine with a focus on the biosphere? The goals are formulated in anthropocentric terms, and e.g., neglects animals (Torpman and Röcklinsberg, 2021). This deficit of the goals when implemented in a biosphere-directed framework should be taken into consideration, but it is already handled by the Wedding Cake Model where the biosphere is the foundation for, but not independent of, both the society and the economy (Rockström and Sukhdev, 2016). This structure has also been used for the design of our sustainability assessment (Table 4).

4.2. Stakeholder and citizen interviews

4.2.1. Concerns for ecology and environment

As stated above, the data from the documents indicate that a biosphere-focused framework is crucial. This view is also well represented amongst the stakeholders and in the citizen groups. One of the main concerns in the interviews with stakeholders are the possible negative impacts on nature and/or wild relatives of the farmed salmon, as well as on how to handle unknown consequences. Ecology-related concerns were expressed by scientists and fish health workers, participants from trade unions, salmon farmers, non-governmental organizations (NGOs), wild salmon management, Sámi resource management, and in Norwegian and Sámi citizen groups (see Table 4). To avoid negative impact on wild relatives and/or the environment by using genome-edited salmon is therefore crucial. The protection of and respect for nature was also used to describe sustainability amongst the stakeholders and citizens (wild salmon management, Sámi resource management, citizen group Norwegian, citizen group Sámi), and adding to this both participants from wild salmon management and salmon farming emphasised how food production and development which is sustainable must be performed "[…] on nature's own premises" (participant from wild salmon management, our translation).

Recently, a sterile salmon has been developed using genome editing and results shows it could be possible to produce brood stocks which are able to have sterile offspring (Güralp et al., 2020). This solution is presented as contributing to reducing the interbreeding between farmed and wild salmon when the farmed salmon escapes. This was shared to the participants in the interviews as one of several applications of genome editing pursued in salmon. Several stakeholders, including wild salmon management and NGO representants pointed to how interbreeding and genetic contamination is not the only problem related to escapees. They argued that the sterile salmon would still escape and

Table 4
Levels are from the rearrangement of the UN SDGs by Rockström and Sukhdev (2016) based on Agenda 2030 (UN, 2015).

Level UN SDGs	*Topics* Control questions
Biosphere 6: Clean water and sanitation 13: Climate action 14: Life below water 15: Life on land	*Ecology* • Does the alteration lead to increased protection/ conservation of biodiversity and/or ecosystems? (BFA, Starfish, FF, NGO, CGN) • Will application effect ecosystem functions? (FHE) • Will application impact wild fisheries or other species, reducing diversity and the use of more "regenerative and equitable practices"? (BFA, Starfish) • Will application of GE technology increase farming activity/intensity at the expense of wild species? (SPS) • Does the alteration lead to reproductive and non-reproductive impact on wild relatives? Reduce genetic variation in wild relatives? (NGAS, BFA, SGE, TUR, SAF, FHW, NGO, SRM, WSM, CGN) • What measures are taken to reduce interaction with wild relatives? (SGE, SRM, WSM) • How will GE technology affect the existing threats/interactions of the fish (e.g., Salmon: predators, escaped farmed salmon, climate change, pink salmon, other pelagic species (competition, predation), habitat destruction? (SPS)
	Impact on environmental pollution (chemicals/ pharmaceuticals) • Risk of selecting for novel pathogens or parasites? (FHW) • Is the use of medical treatments reduced? (SGE) • Does application reduce use of antimicrobials? (FF) • Will the use cause increased pollution? (BFA, NI, SGE,) • Does the new organism require new feed type, and is this feed more, less or equally impacting environment? (NGAS)
	Climate change • Are effects within the planetary boundaries? (NGAS, NI, BFA) • Are there negative impacts on the local/global environment? (SGE, SAF, FHW, TUR, WSM) • Will application improve climate change adaptability of the product/production/supply chain? (FHE, BFA, SPA, CGS) • Will application cause a shift in the distribution and productivity of species as a result of ocean warming and deoxygenation affect pelagic fisheries? (BFA) • Will use contribute to reducing greenhouse gas emissions? (BFA) • Contribute to climate action? (BFA) • Is environmental footprint changed? (FHE, BFA)
	Resilience in food production systems • Does the alteration lead to a production which is more diverse, resilient? (BFA, FF) • Will application increase (biological) diversity in global food production? (FHE) • Will application affect the genetic diversity in the eggs? (FHE)

(*continued on next page*)

Table 4 (*continued*)

Level UN SDGs	*Topics* Control questions
Society 1: No poverty 2: Zero hunger 3: Good health and well-being 4: Quality education 5: Gender equality 7: Affordable and clean energy 11: Sustainable cities and communities 16: Peace, justice and institutions	*Food safety, security and quality* • Improved food safety? (NGAS) • Improved global food security? (NI, NGAS, FHE) • Does the alteration lead to a production of healthier products? (BFA, FHE)
	Justice and equal access • Does the alteration lead to production which is more just? (BFA) • Does application affect the product availability for poorer countries/groups in society, or more affordable? (FHE, ABR, CGS) • Does application of GE organism lead to centralization or spread of ownership? (NGAS) • Are there benefits except economic return? (BFA, Starfish)
	Future generations access to resources • Will the use of GE technology enhance future generations access to wild resources a) in traditional management? (SPS, SPA, TUR), or b) to indigenous cultural nature management? (SPA)
	Consumer and citizen engagement and acceptance • Is there broad public support? (Starfish, TUR, SRM, SAF) • How will the alteration be communicated to (end) consumer? (SAF, SGE) • Have relevant local communities, or groups with activities in the planned release area been consulted? (SPA, SPS) • Will application of GE technology enhance existing conflicts of interests/have negative impact on local harvesting activities? (SPS, WSM)
	Local and indigenous knowledge, rights and traditions • How does the alteration affect small-scale actors, local community and indigenous traditional fishing [possibility to choose another production method in the future, monoculture, impact on area competition]? (BFA, SPA, SPS, Starfish, SRM) • What is the cultural role of wild relative species? (SRM) • Have the Sámi society (if relevant in the area of application) been consulted? (SPS) • Have traditional knowledge been included in the assessment of possible effects on surrounding environment/society? (SPS) • Can indigenous and local knowledge, innovation and practice be preserved and respected by the introduction of the new organism? (SPS, SPA**)
	Gender equality in food production • Will application improve acknowledgement, rights, and positions of women in food production? (FHE)
	Global effects • What are the possible effects in other countries than Norway? (FHE) • Effects on small-scale farmers and fishers in least developed countries? (FHE)
Economy 8: Decent work and economic growth 9: Industry, innovation, and infrastructure 10: Reduced inequalities 11: Responsible consumption and production	*Farmed fish health, welfare and intrinsic value* • Does the alteration lead to improved animal welfare? (NGAS, FHE, FF, SGE, TUR, SAF, FHW, ABR, WSM, CGN, CGS) • What are specific fish health implications? (FHW) • Does the alteration allow for not improving negative conditions in environment? (NGO) • Does the alteration restrain the fish from outliving natural behaviour? (NGO, CGN) • Does the alteration cross species boundaries? (FHW, TUR, SGE) • Is the alteration respecting what changes are already happening in nature? (SGE, FHW) • Is the alteration infringing the intrinsic value of the fish? (CGN, SAF, SGE, WSM)
	Production efficiency • Is production made more efficient? (NI, TUR, SAF, ABR) o Preservation methods of product? (FHE) o Is food waste reduced? (FHE) o Costs reduced? (SAF) • Affect marked access of related products? (NGAS) • Does the production cause increased monoculture, and then possibly reduced resilience? (SGE, FHW, NGO, SAF, CGS)
	Available alternatives • Is the alteration preventative regarding specific challenges? (NI) • What are alternative solutions to the challenge the GE technology is meant to solve? (SPS) • What are consequences of not applying the technology? (SPS (if one technique is banned, will another be used?)
	Employment and economic growth • Does the use of GE organisms cause an increase in employment? (FHE) • Create livelihoods? (BFA)

Abbreviations: GMO (genetically modified organism), SGE (scientist using GE in fish), TUR (trade union participants), SAF (salmon farmers), FHW (fish health workers), NGO (non-governmental participants), ABR (advisory body participant), SRM (Sami resource management), WSM (wild salmon management), CGN (citizen group Norwegian), CGS (citizen group Sámi), NGAS (Norwegian Governmental Aquaculture Strategy), SPA (Sami Parliament area strategy), BFA (Blue Food Assessment), FHE (Food, Humans and Environment), FF (Farm to Fork), SPS (*Sámi Parliament Statement on Salmon*), NI (Federation of Norwegian Industries), **from the Convention on Biodiversity article 8j.

have non-reproductive effects. Bradbury et al. (2020) has also pointed out this concern; an escaped farmed salmon will compete for resources and disturb the mating season. One of the trade union participants mentioned that this ecological impact is relevant as Norway holds 25% of the global salmon stock. After the conduction of the interviews the salmon stock in Norway has gone from being viable to near threatened and is on the Red List (Hesthagen et al., 2021). The main impact factor is human activity, including genetic contamination from escaped farmed salmon and spread of diseases (Thorstad et al., 2021). To preserve the wild salmon stock is therefore essential and implies that one should avoid escapes by salmon in general including the genome-edited salmon that is sterile. One solution to this may be, as suggested by a researcher and in the Norwegian citizen group, to only allow genome-edited salmon in land-based facilities.

4.2.2. Concerns for increasing farming activity

Some participants (scientists, citizen group Norwegians) mentioned terms like self-maintainaing, on-going, self-fuelling, durability and so on, when defining sustainable development. This way of describing sustainability requires that utilization of natural resources do not exceed more than we need, and associates to terms historically used to describe the relation between humans and nature which we today define as sustainable development (Du Pisani, 2006). Further, it indicates a fear of industries, like the salmon farming industry, to grow beyond planetary boundaries. A general concern amongst several of the stakeholders and the citizens (see Table 4) was whether genome-edited salmon would legitimize increased growth in the industry. One of the salmon farming participants expressed it as a risk of creating "[…] an evil circle" (our translation) as symptoms of a problem in the industry is removed, it will allow to increase the production. At present salmon farming in Norway is mainly monocultures, thus increasing the production intensity will lead to the bloom of new, and possibly unknown diseases (Grefsrud et al., 2022), hence solutions provided by genome editing can be considered only as short term solutions if not combined with mechanical solutions and systems changes.

In the Sámi citizen group, this was pointed out by that "[…] nature is long-term, economy is short-term" (our translation). This is an argument which is based on a general critique against aquaculture or a scepsis towards industries driven by profit, it is independent of genome editing, but more directed to the system it is going to be used in. But it also gives some directions for how to solve present challenges. In a recent article by Rosendal and Olesen (2022) discussing the lice problem, they ask why there is so little attention to strategies that promote public good, as for example breeding strategies including the use of genome editing. They point out that the main focus on the problem has been on innovation in novel ways of treatments by chemicals or mechanical devices, increasing pollution and decreasing animal welfare. This illustrate that the industry needs to take a more systematic long-term approach and consider sustainability through its own activities as well as effects on the surrounding environments. Introduction of new farming activities or the use of genome editing may in such a context need to *consider whether the change creates positive effects, not only avoid or reduce present negative effects. In the conversations with stakeholders and citizens, positive contributions to human health, fish welfare and reduced environmental impact is crucial for acceptance of genome editing, as stated in a Norwegian citizen group:* "It should be good for all involved" (our translation).

Looking at the publications by BFA it is evident that the farmed salmon can contribute to, but is not as a crucial product in, global food systems (BFA, 2021). The work shows the importance of several other aquatic animal groups and of combining groups in the diet to ensure diversity of nutritional intake (Golden et al., 2021). This indicates that using genome editing in aquaculture should be combined with farming and aquaculture practises that contribute to increasing the diversity in species. Second, the importance of small-scale actors, including indigenous groups, in both farming and fisheries should be acknowledged, as diversity is "[…] key to the future of aquatic food systems" (Short et al., 2021).

4.3. Local and indigenous knowledge, rights, and traditions

The Norwegian governmental and the Sámi Parliament documents do all have a long-term focus, and aims at ensuring future generations access to resources, but the means on how to achieve such development is different in the context of how to utilize the oceans and waters. Sustainability in the strategy by the Ministry of Trade, Industry and Fisheries (2021) is described as "[…] the world becomes a better place for the humans living now, without compromising the possibilities of future generations" (our translation). The Sámi Parliament Statement on Salmon builds on politics grounded in values of "respect for, knowledge about and connectedness (*nærhet*) to nature" and "The management of resources is done in a long-term perspective focusing on future generations possibilities" (Sámi Parliament, 2021), our translation).The concepts of reciprocity, care and connectedness to nature is according to Mazzocchi (2020), found in general in relation to indigenous knowledge.

The Norwegian governmental aquaculture strategy states that environmental impacts from aquaculture must be reduced as much as possible, and Norwegian seafood [farming of salmon] is an important part of global food security (Ministry of Trade, Industry and Fisheries, 2021). The Sámi Parliament Statement on Salmon emphasizes that aquaculture cannot exist at the expense of wild salmon fisheries, but the situation today is that farming of salmon is threatening the wild salmon stocks (Thorstad et al., 2021) and thus Sámi traditional harvesting (Sámi Parliament, 2021). This conflict is also described in the Sámi Parliament Statement on Area (2016) with regards to how withdrawal of access to nature area conflict with Sámi traditional use of local nature. This management is based on that "[…] anyone who uses nature (*utmark*) have to be aware of their responsibility for preserving nature for future generations" (Sámi Parliament, 2016, our translation). Both Sámi Parliament statements also emphasize the lack of including traditional knowledge in Norwegian Governmental management strategies, and this conflict is also described by e.g., Joks and Law (2017). Traditional knowledge should be used in evaluations of natural resources in addition to scientific knowledge because it is an expression of the experience of generations, which is required in the Convention of Biological Diversity article 8j (CBD, 1992) and demanded by law in the Norwegian Nature Diversity Act of 2009 (Ministry of Climate and Environment, 2009). Impact on indigenous and local people's culture and traditions by the use of gene technology, is however only included in the final ethical assessment checklist under the GTA (Ministry of Climate and Environment, 2005). An improvement would be to include indigenous views and knowledge of natural resources into a sustainability assessment too.

In the Sámi citizen group, sustainability was perceived in different ways. One of the participants said that "Sustainable development now, in an industrial society, is more about not using too much of the earth resources. But when I think about original Sámi sustainable development, that is about it staying, right, that the highlands and the forest shall remain as it is […], it is about not disturbing nature" (our translation). Another participant answered that "[…] we cannot live as our ancestors did, so now it is about reducing the footprint, because we leave footprints, that's just how it is, but [we need to] be aware of how to reduce the footprint, and [prioritize what footprint to make]" (our translation).

Empowering indigenous groups is included as one of the actions suggested by the Blue Food Assessment policy strategy (BFA, 2021). Including and applying Sámi resource management could be of great advantage as an important concept in Sámi resource management is expressed in the word *birgejupmi* – to get by (*å greie seg*) (Sámi Parliament, 2016). The concept aligns with the concept of planetary boundaries – both are about how humans should get by within the capacity of nature. The conflict between Sámi nature management and salmon farming was also emphasised by one of the wild salmon management participants in interview. S/he explained the term *birgejupmi* by how the farming industry is expanding at the expense of wild fish stocks, and this reduced the ability of the wild fish to also get by. This is associated to thinking about sustainability where the biosphere is prioritized and respecting the planetary boundaries is the main way to achieve a sustainable development.

4.4. Animal welfare as part of sustainability

The previous published reports and articles on sustainability assessment of GM plants include animal welfare in terms of impacts on animals by GM plant-based feed (see Table 1). Regarding a genome-edited salmon or fish, it must be re-assessed in terms of how to include animal welfare in the assessment. Looking at the interviews, we see that most participants expressed a concern for the welfare and health of fish (see Table 4), and for several, this should be of main priority when considering using genome editing or not. Both in terms of not enhancing negative welfare impacts already present in the farming of fish, and second to consider applications of genome editing which would improve welfare directly. Some also included animal welfare when defining what sustainable development is (NGO participant, wild salmon management, scientist, fish health worker and in the Norwegian citizen group). The importance of welfare of fish has also recently been emphasised both in the European Commission communication "Strategic guidelines for a more sustainable and competitive EU aquaculture for the period 2021 to 2030" (2021) and in the "European Group on Ethics in Science and New Technologies opinion on the Ethics of Genome Editing" (EC, 2021). We have placed this topic under pillar economy as it includes the SDG 12: *Responsible* production and consumption.

Welfare is connected to sustainability by two routes. First, bad welfare will impair on the production, as pointed out by most of the stakeholders and citizens when talking about animal welfare. Second, an animal welfare NGO and a representant from fish health research (designated to group fish health workers) emphasised how bad welfare is not sustainable *in itself*. This has also been stated by Broom (2010), and we have discussed this connection in a previous book chapter (Blix and Myhr, 2021). When sustainability is defined as something that should be possible to continue doing for a long time (definition also used by stakeholders from e.g., research on genome editing, environmental NGO, wild salmon management), unethical treatment of animals cannot be accepted in what is to be a sustainable production. Animal welfare indicators are also the most used indicators in global certification standards, as shown by Amundsen and Osmundsen (2018), and recently included in an animal protein production sustainability assessment framework by Broom (2021).

Originally, the sustainability guideline document by the NBAB (2009) claimed that the intrinsic value for nature should be included in an ethics assessment, not sustainability. In Norway, the farmed salmon is protected by the Animal Welfare Act (Ministry of Agriculture and Food, 2009) which states that all animals have intrinsic value. Operationalising this in a sustainability assessment could be supported by the Sámi Parliament statement on area stating that nature and all living in it should be respected as part of a sustainable management. The importance of intrinsic value of fish was also raised in stakeholder groups of salmon farmers, scientists, wild salmon management, citizen group Norwegian, and citizen group Sámi. How this could be operationalized is discussed by Trøite and Myskja (2021) stating that including intrinsic value of salmon in farming would require either to abolish the whole industry or to make sure the production is adapted to species-specific behaviour of salmon. Whether genome editing can be used to promote the latter solution, should be further discussed, and was also brought up in the Norwegian citizen group by one of the participants stating that sterility would not be part of respecting natural behaviour of the salmon.

5. Conclusion

In this work we have used global and Norwegian strategy documents for sustainability, and interviews with stakeholders of salmon farming industry and citizen groups to generate a sustainability assessment framework for genome-edited salmon. Table 4 presents the final topics and control questions identified in documents and interviews. Topics to be included in a sustainability assessment of genome-edited salmon are:

- Biosphere: ecology, impact on environmental pollution, climate change, and resilience in food production systems,
- Society: Food safety, security and quality, Justice and equal access, Future generation access to resources, Consumer and citizen engagement and acceptance, Local and indigenous knowledge, rights and traditions, Gender equality, and Global effects,
- Economy: Farmed fish health, welfare and intrinsic value, Production efficiency, Available alternatives, and Employment and economic growth.

For all topics, both local and global impacts should be considered when relevant, and long-term effects must be included. We urge the need to focus these assessments of impacts on the biosphere as a main prioritization as this creates the foundation for sustainable society and economy, both in short, but especially in the long-term and on both local and global level. Our findings indicate that discussing sustainability assessment through the lense of resilience would be an appropriate next step as it could contribute to the development of more sustainable fish farming and food production systems. It would also be valuable to apply the suggested framework on specific cases of genome-edited salmon or other finfish species to identify any challenges and/or missing topics and control questions.

The main result is that approval of a genome-edited organism should be based on questions that gives information on whether the commercialisation could enhance, preserve, or at least not have a negative impact on the resilience in the ecosystem where it is to be released in or can escape to. This is reflected in documents analysed and interviews held as they focus on environment, ecology and climate. We also find it in how documents, stakeholders and citizens define sustainability, where descriptions often return to how the Earth is the main foundation and should be protected and respected. As argued by Amundsen (2022), the understanding and implementation of sustainability is limited to the questions asked in the assessment. This is also the limitation of this framework. However, by grounding the whole framework in the Wedding Cake Model (Rockström and Sukhdev, 2016) and prioritizing the planetary boundaries and on *what creates resilience* we aim at giving the framework a consistent basis for how to understand sustainability, which aligns with the documents and stakeholder and citizen views. The discussion could be continued in a study of how resilience can be a key for the assessment of genome-edited salmon.

Second, the framework should include the topic *Local and indigenous knowledge, rights, and traditions.* In an indigenous understanding of sustainable development, in this case the Sámi understanding, it builds on generations of experience utilizing nature with the intention of ensuring resources of future generations. This can be associated to how respecting the planetary boundaries is the main way to achieve a sustainable development. In addition, some wild species like the salmon are highly significant to the preservation and development of indigenous and local cultures, and in some cases crucial for survival. Indigenous and local knowledge, rights and traditions should therefore be considered in a sustainability assessment of genome-edited fish.

Third, animal welfare should be included in the sustainability assessment because good animal welfare is important for an efficient production and because a system cannot be sustainable if it contributes to animal suffering and thus a more evil society – it cannot be accepted (Olesen et al., 2011), not in short nor in the long term.

Finally, we want to emphasize that this framework aims to contribute to building resilient and diverse food systems, terms often used in the strategy documents. Both resilience and sustainability build on the idea of ensuring the best conditions for humans and environment, under "[…] normal and extreme operating conditions" (Marchese et al., 2018). This framework should be further developed to provide an assessment which is flexible with regards to the control questions used to make case-by-case decisions, but also focused and specific to ensure all assessments are done with the aim of ensuring that genome edited fish contribute to building resilient and diverse food systems.

Ethical considerations

The interviews conducted for data sampling to this paper has been submitted to the Norwegian Centre for Research Data (NSD), reference number 707095. NSD approved the interview guide, the plan for recruiting participant groups including citizens, and data management plan. All participants to in-depth interviews signed declaration of consent for the use of data generated in the conversation. Participants in group interviews were recruited by IPSOS AS and have signed a standard declaration about GDPR and how data is stored generated by IPSOS AS. All participants are de-personified in the analysis of the data as some information about their occupations could indicate individual people. Most participants involved will not be identifiable based on occupation (in-depth interviews) and are therefore considered anonymous. Data are not openly available outside the project group.

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CRediT authorship contribution statement

Torill B. Blix: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Anne I. Myhr:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Paper III

Social acceptance of CRISPR in salmon farming industry: what is at stake?

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Abstract: The genome editing technology CRISPR is potentially an ethical game-changer because of its ability to engineer traits in living organisms without crossing species. Using salmon aquaculture in Norway as a case, we analyse considerations related to the use of CRISPR in salmon farming identified in interviews with stakeholders and citizens. We find that main concerns are related to the environment and fish welfare, and that moral objections formerly raised against genetic modification technologies are still present in discussions of CRISPR. The broad potential of genome editing indicates that case-by-case assessments of sustainability and socio-ethical concerns is required for acceptance.

Keywords: genome editing, CRISPR, salmon, social acceptance, animal ethics, sustainability

Introduction

The novel genome editing technology CRISPR holds the potential to change the landscape of animal breeding because it is cheaper, more versatile and more precise than previous genetic modifications (GM) technologies (Hallerman et al., 2022). In contrast to other GM technologies, CRISPR does not require – but does not exclude - the insertion of foreign DNA and enables rewriting of the genetic code, thus altering the traits of any organism. This creates novel opportunities in agri- and aquaculture, where the technique can be used to adapt plants and animals to make them more fit for production purposes. As CRISPR is implemented in breeding strategies, society and regulatory authorities must take a stand on acceptable uses. Can the use of CRISPR be socially and morally acceptable, and if so, under which conditions?

One area which exemplifies both the opportunities and the challenges brought forth by CRISPR is industrial salmon farming. Seafood is frequently pointed to as an important part of the transition to a more sustainable food future. Norway has ambitions to become the world's leading seafood nation, and Atlantic salmon (*Salmo salar,* from here: salmon) plays a key role in reaching this goal (Ministry of Trade, Industry and Fisheries, 2021). However, several challenges with regards to animal welfare and ecological impacts stand in the way of further expansion (Afewerki et al., 2022). The farmed salmon frequently suffer from viral and bacterial disease and salmon lice, the treatment of which causes suffering and pain (Sommerset et al., 2022). One of the most important environmental threats of the industry is escaped farmed salmon, who breed with the wild populations, leading to genetic introgression and potential constraints on their viability (Bradbury et al., 2020; Grefsrud et al., 2022; Thorstad et al., 2021). In 2021, wild salmon was listed as a threatened species in Norway for the first time (Hesthagen et al., 2021), and it has been shown that escapees are a major cause for this (Thorstad et al., 2021).

To solve these problems, many point to CRISPR as a potential solution. There is ongoing research using CRISPR in salmon to induce sterility in farmed populations to eliminate the negative impact of escapees (e.g., Güralp et al., 2020; Wargelius et al., 2016), and induce resistance against parasites and diseases (Barrett et al., 2020; Nofima 2021a,b). The potential use of CRISPR in salmon farming presents a paradigmatic case for the consideration of using CRISPR on animals: On the one hand, it might solve substantial welfare and environmental problems, but on the other, it raises questions about moral and social acceptability of altering animals´ genetic code.

These questions are not new: Discussions on GM have been ongoing for decades, with extrinsic concerns about risks to health and environment and intrinsic concerns about the moral impermissibility of intervening in nature in this way (Myskja, 2006). In the past, such GM technologies have been met with skepticism in European populations (Gaskell et al., 2011). Safety for humans and environment, absence of benefits, uncertainty and unintended consequences, and social, moral and ethical issues as well as lack of trust in relevant actors and institutions are reported to be important public concerns (Frewer et al., 2004; Frewer, 2017; Kamrath et al., 2019; Lassen et al., 2002). Core to this is the understanding that the crossing of species in GM technologies is morally wrong and represents qualitatively new risks (Lassen & Jamison, 2006).

However, CRISPR holds the promise of changing the scene of this discussion. Since no transfer of genetic material between species is needed, one of the main public objections against GMOs appear to be met. There are therefore high hopes that this technology will be positively received by the public (Yang & Hobbs, 2020), and on this account, CRISPR is sometimes presented as an 'ethical game-changer' (Schultz-Bergin, 2018, p. 222).

Whether or not CRISPR is a game-changer is important for ongoing debates about how the technology should be regulated. Should CRISPR as a genome editing process be regulated under current GMO Acts and directives with its lengthy approval process? Or should the organisms that are the products of CRISPR be considered no different from ordinary products and therefore merely be part of ordinary food safety regulation? (Hallerman et al., 2022) This controversy of *process* or *product* has been going on for several years and form one backdrop for the relevance of this study. Even if scientific consensus could be established about this matter, public acceptance of CRISPR is necessary for ensuring legitimacy of its application in salmon farming (Yunes et al., 2021).

There is still little to be found in the literature on the ethical challenges and implications as well as on public acceptance of using CRISPR to engineer animals (Bartkowski et al., 2018, p. 173; Frewer et al., 2014; Schultz-Bergin, 2018, p. 222). Policy reports, scientific literature and guidelines for risk assessment regarding regulation on genome editing in agriculture focus on plants (Ciabatti, 2021; Friedrichs et al., 2019; Okoli et al., 2021), with some exceptions (see e.g., De Graeff et al., 2019). Former studies on acceptance of GMOs suggest that consumers are generally skeptical towards GM animals, with some of the reasons including environmental hazards and animal welfare and integrity (see, e.g., Behgin & Gustavsson, 2021; Bredal, 2003; Frewer, 2003; Grunert et al., 2001; Han, 2007; Marques et al., 2014). Very little research exists on public acceptance of CRISPR on animals and results vary between finding low (Yunes et al., 2021) and higher acceptability (Gatica-Arias et al., 2019; Tadich, 2022), depending on the objectives for use or traits targeted.

Fish, and particularly salmon, present an interesting case: The wild salmon is an important ecological species with an iconic status (Myskja & Myhr, 2012), in both Norwegian and Sámi culture (Myrvold et al., 2019; Rybråten & Gómez-Baggetun, 2016). Farmed salmon, on the other hand, is produced in a large-scale industry, swimming in crowded circles in pens, referred to as biomass and measured in tons. While other candidates for genome editing, such as cattle and pigs, evoke empathy as individuals, farmed salmon can be understood as border animals between mammals and natural entities (Bovenkerk & Meijboom, 2012). Arguably, fish tend not to evoke the same moral concerns as other animals, not because people lack knowledge about fish sentience and abilities, but as a result of the difficulty for humans of having meaningful relationships with fish (Driessen, 2013). In other words, though the cognitive abilities of fish often match or exceed that of other vertebrates (Brown, 2015), this seems not to have translated to increased compassion or concern for their welfare. As Driessen puts it, 'they are quintessentially non-cuddly animals, cold, slimy, and with their unblinking and sideways directed eyes they don't have a "face" to us.' (Driessen, 2013, p. 1) In Norway, in the past, it was common to claim that fish, in fact, are not animals (Medaas et al., 2021, p. 29). This perception, however, has changed in recent years (Lien, 2015; Medaas et al., 2021, p. 29), but more knowledge is needed about how this is reflected in acceptance of genome editing.

To contribute to the knowledge about acceptability of using CRISPR in animals, we report from a study addressing social acceptance related to the use of CRISPR in salmon farming. Based on 19 interviews with stakeholders within or connected to Norwegian salmon farming and four focus group interviews with citizens, we ask how people understand CRISPR technology and which uses of it they see as acceptable in Norwegian salmon farming?

In the following, we first describe our study design, and thereafter present results regarding views on genome editing technologies and considerations about its use in relation to the environment and the wild salmon, as well as to the farmed salmon. We then present study participants' views on how genome editing could potentially be used in the salmon farming industry, and which demands should be fulfilled to deem such uses acceptable. We discuss how our findings relate to earlier research about public acceptance of GM and genome editing technologies and end the article with some perspectives for further research and policy.

Methods

The study was conducted as part of a larger research project about conditions for social and moral acceptability of genome-edited salmon (CRISPRsalmon: https://www.ntnu.edu/crispr-salmon). The study design includes individual, qualitative, semi-structured interviews with stakeholders in the salmon farming industry and focus group interviews with citizens.

Recruitment of participants

Table 1 shows the number of participants from each stakeholder group and in citizen focus groups. Relevant stakeholder groups were those directly or indirectly related to the salmon farming industry in Norway, including people from protection and/or management of nature, wild salmon, and from research on genome editing in and/or health of fish. Thirty-eight individuals holding leading positions within these groups were invited by a letter containing information about the study, and 19 accepted the invitation. Participants in the focus group interviews with citizens were recruited from different regions in Norway by the market analysis company, IPSOS, seeking maximum variation according to age (18-80), gender, ethnicity, and geographical location. For one group, individuals with Sámi background in addition to these criteria were recruited. All recruited focus group participants received a compensation of 500 NOK (49 Euro).

Table 1 Interview groups with number of interviews per group. For citizen groups the number shows number of groups x number of participants per group.

Groups	Number of interviews
Scientists using genome editing in fish	4
Trade union participants	2
Salmon farmers	4
Fish health workers	3
NGO participants	2
Advisory body participant	1
Sámi resource management	1
Wild salmon management	2
Focus group Norwegian	3 x 6 participants
Focus group Sámi Norwegian	1 x 6 participants

The interviews

The interviews covered both personal experience, views and reflections related to salmon and its welfare, genome editing, and the sustainability of salmon farming.

For the discussion about genome editing, participants were given a short, popularised description of what CRISPR is, and how it has been used thus far in research: generating sterile salmon, holding the potential to generate disease resistance and increased omega-3 content, and growth. For the discussion about sustainability, we used a more open approach asking participants to elaborate what the meaning of sustainable development was to them and how this would relate to using genome editing in the salmon industry. A semi-structured interview guide (Flick, 2009, p. 150) was used to help structure the interviews, but order and wording of questions and probes were flexible and used to encourage participants to express their views freely and in their own words. Due to the Covid situation all interviews were conducted online over Zoom or Teams. The stakeholder interviews lasted for about an hour and were conducted by the first two authors. The focus group interviews with citizens were moderated by the first two authors, with representants from IPSOS solving practical matters and taking notes. The focus groups lasted between 1 hour 10 minutes, and 1 hour 37 minutes.

All interviews were audio recorded and transcribed verbatim.

Analysis

The interview transcripts were coded following standard social science principles (David & Sutton, 2011, p. 338-61) including both deductive and inductive approaches. First, pre-decided index coding was used to thematically organise the data in accordance with the themes of the research questions and the interview guide (Coffey & Atkinson, 1996). The focus was on identification of views regarding the use of genome editing technology on farmed salmon. In a second more inductive round we focused on additional themes that emerged from the data during analysis and on specifying considerations. The coded segments were then analysed by meaning condensation (Brinkmann & Kvale, 2014, p. 231-235) resulting in a list of statements which were categorized into the following themes: concerns regarding the CRISPR technology; concerns regarding the wild salmon and the environment; concerns regarding the farmed salmon, and demands to the product and the industry, and views on potential uses of CRISPR technology. The first two authors conducted the analysis in collaboration with last author.

The Norwegian Centre for Research Data (NSD) was notified before the sampling and use of personal information (NSD reference number 707095). All stakeholder participants signed a declaration of consent. IPSOS AS arranged standard declaration about GDPR and data management with focus group participants.

In a previous publication (Blix & Myhr, 2023) we compared stakeholder views on sustainability of genome-edited salmon with sustainability strategies formulated in policy and strategy reports. Here we present a broader thematic analysis of the findings from the interviews and focus groups. Earlier research has analyzed how understandings of gene technology differ between various actors (Bain et al., 2020; Robbins et al., 2021). Here, we explore views on CRISPR among a broad variety of actors and citizens. Our aim is not to analyze differences between actors, but to unfold the range of considerations about the use of CRISPR in Norwegian salmon farming which is articulated among a differentiated group of stakeholders and citizens.

Results

In the interviews marked differences between stakeholders and citizens were found with respect to the level of knowledge about the use of genome editing in the salmon farming industry. While some stakeholders showed detailed knowledge about CRISPR, participants in focus groups often expressed themselves with hesitation or doubt. Despite such obvious differences, most participants were able to express opinions about the themes of the interviews. In the following, we present our results moving from general understandings of genome editing technology, such as CRISPR, to more specific considerations about potential consequences of using such technologies in Norwegian salmon farming and from there to more concrete deliberations about under which conditions such use could be meaningful and acceptable.

Concerns

The difference between CRISPR and GM

A narrative that was both affirmed and challenged in both the stakeholder and citizen interviews was the idea that CRISPR is a more natural technical tool than older GM technologies or traditional breeding. For example, one scientist pointed out that the idea of naturalness is ‘highly debatable’, though s/he described CRISPR as a ‘fast track of the natural selection’. Some participants saw CRISPR as the natural next step in breeding technologies, while others questioned its radicalness. One of the participants argued that the advantages of CRISPR is that it does not require inserting genes from other organisms, even though such an application is possible. Several participants from science, trade unions, salmon farming, and fish health service expressed concerns about crossing species. For example, one of the wild salmon management participants stated that ‘genetics makes us who we are’, signalling that inserting genes from other organisms would make the salmon into something that it is not today. A fish health researcher indicated that crossing different salmonid species would be more acceptable than crossing with less related species. Other participants were more open to crossing species but referred to the market as a problem: ‘It might be old attitudes […] and might change over time […] [but] I know that it will be a challenge with regards to consumer acceptance, anyway.’ Discussion in the focus groups confirmed this, but there were also some focus group participants who did not think it mattered how the salmon was genome edited. ‘As long as the fish I buy in the shop is good, I don’t care,’ as one participant from the focus group put it.

It is often argued that the less invasive character of CRISPR leads to organisms with traits like those found in nature, e.g., with disease resistance and sterility. A fish health worker emphasised that changing genes that would not mutate naturally increases the risk of negative impact. A scientist using genome editing in fish appeared to agree:

> If we use genome editing to just, you know, change the genes in the animal so that they are like these naturally resistant animals, then I am very comfortable with it. [...] Whereas if someone […] made a protein that just chopped the sea lice or something like that and inserted this into the gene for the salmon I would be very uncomfortable it because it's not something that is naturally occurring.

Concerns about our ability to predict unforeseen effects were also raised by several participants. One of the scientists captured this worry with a compelling metaphor:

> When you start thinking about making a salmon resistant against viral attacks, there are so many genes being upregulated and downregulated and signal pathways going here and there and criss-crossing, so it might be as if we were to take a city metro map in London or New York, throw it on the table and shut down one station and think it would only affect the green line and then you see oh shit, something happened in the orange and purple line that we had not thought of.

Some of the scientists also pointed out the risk of reducing the genetic diversity in the farmed stock, thus reducing its resilience. One of the scientists stated that '[…] we don't want to stop with one edited fish and lose all the genetic variation that is in the population.'

The wild salmon and the environment

While many participants confirmed the potential benefits of using genome editing technologies on farmed salmon, concerns about potential negative impacts on ecosystems, and particularly on wild salmon stocks, were widely shared. Environmental concerns were often expressed rather vaguely, for instance by merely contrasting the environment to the laboratory and arguing that while it is unproblematic to do experiments in the lab, it is important to 'keep nature clean'. 'What will happen […] if the technology is released in nature?' a participant asked. No specific worries about potential negative impact on nature were pointed out, rather the participants seemed concerned about unforeseen effects on ecosystems in general. In keeping with this, some participants argued that a genome-edited salmon should be kept away from any possible interference with the surrounding environment and only be produced in land-based facilities. One fish health worker maintained that this concern is relevant not only for genome-edited salmon but for salmon farming production in its current state.

The greatest concern among stakeholders was the possible consequences of having genome-edited salmon escaping from the pens and impact the wild salmon populations through interbreeding. Some participants described the wild salmon as 'iconic' and as an important species in Norwegian culture that Norway has a responsibility to preserve. In all conversations about this, wild salmon was valued higher than the farmed salmon both in terms of food quality and status. Some participants, both stakeholder and citizens, were eager fishers in their leisure time, and felt they had a significant relationship with wild salmon for this reason. Among the participants with a Sámi background, several pointed to the important role it plays in their culture. When participants were informed about using CRISPR for making the salmons sterile to avoid interbreeding, concerns about possible unwanted consequences of other interactions with the wild populations were also raised. One representative for a wild salmon management organization pointed out that even if the farmed salmon was sterilized, it could still transfer diseases and constitute a threat towards the wild population through increased competition for food and breeding spots. Wild salmon might still try to breed with the farmed salmon, but this would be 'wasted work, [the wild salmon] loose both partner and ability to reproduce because it has wasted resources on nonsense.'

The farmed salmon

It was a shared view that applications of CRISPR on farmed salmon must be consistent with a good treatment of the salmon: 'Obviously if you generate a farmed salmon that is worse off, this will not be acceptable,' a participant stated. Some made stronger demands that CRISPR should not only keep the status quo but must actively improve the welfare of the salmon: '[…] it must be clear that the positive effects are significantly larger than the negative, it has to be significantly bigger.' Avoiding diseases and salmon lice were frequently pointed to as examples of alterations that may have considerable benefits, but concerns were raised that genome editing the farmed salmon might cause negative impact on welfare that we cannot currently foresee. Some introduced broader notions of welfare where it was not merely taken to mean the absence of pain and disease, but rather allowing the fish to be able to perform their natural functions and live a good life.

Participants were asked about their thoughts on the intrinsic value of the farmed salmon in relation to the use of CRISPR. This was a complex question to address, as the 'intrinsic value' was often seen as a difficult concept to define. While many participants argued that use of CRISPR must not infringe upon the intrinsic value of the salmon, they had diverging understandings of what this requirement means. For an NGO stakeholder, for example, respecting the intrinsic value of the fish is principally incompatible with industrial salmon farming in its current state, and possibly with farming fish at all:

> [The intrinsic value] is clearly not being taken into consideration at all. [...] The Animal Welfare Act says that the individual and species-specific needs of the animals should be taken into consideration. And that is just nonsense. There is such a big contrast between the law, which has some really nice phrases, and we can be proud and say we have one of the best phrased animal welfare acts in the world. […] But it is allowed to keep animals in tight spaces that in no way satisfy their individual and species-specific needs. And farmed salmon is the worst example. Things are bad for agricultural animals too, but it is somehow particular to fish that they are not really considered to be animals at all.

Other participants also argued that domestication on some level interferes with intrinsic value, since the animal is designed to fit our needs. In these discussions, the interviewees would compare the intrinsic value of the farmed salmon to that of the wild. It became clear that some of the participants found that the wild salmon has a higher status than the farmed, and some participants even argued that it has a higher intrinsic value. However, the 'lesser value' of the farmed salmon does not imply that anything goes in terms of what should be allowed to do with it, and genome editing should not change norms for acceptable treatment. One salmon farmer commented that '[...] breeding has been going on for centuries, so it has affected the intrinsic value of the animal.' However, 'I think that even if the animal has been gene modified, you have to show respect for it.' Even though its status was lower than that of the wild salmon, some argued that our responsibility for the farmed salmon might be higher than the responsibility we have for the wild salmon, since it is us who have brought it into existence. Salmon farmers noted a high concern for the well-being of the farmed salmon, and a fish-health worker described it as 'painful' whenever there is a health issue in one of the pens. As s/he put it: 'I'm supposed to be there for the fish. It sounds weird to say it out loud, but it is an animal, and it has feelings, and it shouldn't feel any pain and [it should] be ok, and that is our job.' In other words, respect for intrinsic value was related to the well-being of the salmon and to respectful treatment of it, which is not necessarily incompatible with genome editing.

Views on potential uses of genome editing in the salmon farming industry

Sterility

Using genome editing to produce a sterile salmon was found to be potentially acceptable, since it could contribute to protecting ecosystems. This appeared more acceptable than e.g., using genome editing for increasing growth or other commercially related traits. Several stakeholders stated that the motivation to preserve the wild salmon in its pristine state should be the prevailing priority. But still, as shown earlier, various stakeholders questioned the introduction of sterility and raised questions about problematic interaction between farmed and wild salmon, such as competition for feed and disturbance of mating. There were also concerns about the farmed salmon and how sterility would affect its life quality and overall well-being.

Lice resistance

In line with this, producing a salmon lice resistant salmon was highlighted as an example of a welfare induced use of genome editing that could be acceptable. Yet again, from wild salmon management a warning was issued: ‘How will that affect the salmon lice as a pathogen to the wild salmon? We know very little about that’, concluding that ‘making fast changes might not be very wise’. At the same time, a trade union participant emphasized the potential benefits to the industry: A salmon lice resistant salmon would be ‘the farming industry getting a Christmas present for the next 50 years’.

Enhanced growth and efficiency

Participants were divided about using CRISPR to enhance growth and increase efficiency. In the focus groups, it was pointed out that we need to ask who we are doing this for: the animal or the industry and ourselves. One participant argued that we need to differentiate what we do to solve and prevent problems in the salmon farming industry and what we do to increase efficiency. Concerns were also raised about how increased growth could impact welfare and general quality of life. It was stressed that such applications should not be a priority. Among some of the participants from the salmon farming industry and their trade union, on the other hand, increased growth and more efficient utilisation of feed was seen as a positive applications of genome editing. This was echoed by one of the scientists, who stated that if increased growth would not induce health issues it could reduce disease as it would reduce the time the salmon is exposed in the sea.

Conditions for product acceptability and demands to industry

Participants considered it crucial that the general public must find genome-edited salmon acceptable for it to be introduced on the market. One researcher insisted that the majority should accept it, and a Sámi resource management participant emphasized the need to confer with minorities as well: ‘It has to be socially sustainable here by us, people have to understand what this is, what it implies, and what the advantages and disadvantages are before we apply it.’ At various points during the interviews specific conditions were put forward for how genome-edited salmon could become an acceptable product. A prerequisite often brought up, but almost taken for granted, was that genome-edited farmed salmon must be safe for humans. Participants did not seem to worry about safety but demonstrated a high level of trust in public authorities on this point. Discussions in the focus groups implied an understanding that if a genome-edited salmon is put out on the market, its safety would already have been established.

Furthermore, the product must be labelled, as people should have the opportunity to choose whether or not to eat genome-edited salmon. Labelling was thought to potentially generate negative associations as genome-editing is controversial. A fish farmer worried that GMO-labelling could create uncertainty among consumers and found it a challenge, that ‘No one demands GMO fish, right?’

A way forward could be to ensure that the product is cheap and accessible. A stakeholder participant explained about the low-price market: ‘I think in that part of the market people don’t care about what they eat, as long as state authorities have approved it, people will buy it.’ While higher up in middle class markets, ‘[…] you meet issues of principle.’ Another stakeholder argued that in order to sell, a genome-edited salmon probably must be more accessible and significantly cheaper than other products on the market.

The interviews also highlighted concerns related to the salmon farming industry itself. A general principle emerged that genome editing should not be used to obscure or enhance the negative impact on welfare and nature that the salmon aquaculture already poses in Norway. In one focus group, for example, it was stated that a genome-edited salmon will not solve all the impacts the farming industry has on nature, and an NGO stakeholder said '[in a production facility], it is not the animals creating the problems, it is the environment around them. As an organism you react to a bad environment.' S/he also emphasized that the fish not only has a physiological process with disease, but it also experiences the bad farming conditions which are not removed by removing disease. Similarly, making the salmon sterile does not reduce the number of escapees, it only prevents interbreeding with wild stocks. This was therefore a good example of 'symptom-treatment'.

Following from this, another argument was that genome editing should not be used to increase production intensity. Participants were aware that a desired outcome for the industry, and therefore a possible consequence of changing traits in the salmon, would be an increase in production. For many stakeholders and citizens, however, this was a concern. One of the salmon farming participants argued that we may enter a 'vicious circle' if we introduce traits such as sterility and lice resistance, as it could potentially lead to increased production intensity, 'which again leads to other things'. As an example, a scientist said that s/he would object to their research on viral infections being used to increase stocking intensity. The fact that the fish are less prone to catching diseases in tight spaces thanks to their research should not mean that the fish are offered less space.

It follows that in general, welfare should never be compromised on account of potential economic benefits. More specifically, changing traits for improving welfare should be prioritized before e.g., increasing growth and increasing production intensity. One citizen in the focus groups suggested that a distinction should be made between changes which reduce and eliminate problems, and changes which increase efficiency. A citizen also stated that s/he 'would feel safer if it was something based on science, not profit'. In one focus group, a participant said that 'sustainability and fish health create the economy, not the other way around.'

In line with these concerns, several participants considered it reasonable to seek other solutions before applying genome editing. An NGO participant argued that the environment within the pens should be changed before anything is done to the animals, and stakeholders from science suggested to change the feed before we change the fish. A participant from wild salmon management said that genome editing should be a last resort, and that the industry should rather consider scaling down the production:

> If we are to start genome editing to adjust the load we have imposed on the farmed fish. Then I think that [for] Norway, with its wealth, there are other measures which should be applied. For example, we could be more modest, maybe. Halt the development a bit, change the modes of operation. It could cost us a bit more to produce one kilo of salmon, but that salmon fares better. And it will have a smaller environmental footprint, that's my main thoughts on that. This may be the reason I am a bit against applying genome editing. […] Something tells me it is for our profit we do it, we won't starve if we stop producing a million tons farmed salmon, I think we could produce a bit less.

Discussion

In this study, we explored views on genome editing technology and its potential use in the Norwegian salmon farming industry, as expressed in qualitative individual and focus group interviews with stakeholders and citizens. Our results partly corroborate results from earlier Norwegian surveys by Bugge (2020) and The Norwegian Biotechnology Advisory Board

(NBAB, 2020); that many Norwegians are positive about using genome editing in Norwegian agriculture and aquaculture for purposes that are perceived to promote societal benefit and sustainability. However, here we qualify this with nuance and add some reservations.

We found both positive and negative attitudes to the use of genome editing in Norwegian salmon farming. Some highlighted the promises of this 'fast track of natural selection' and underlined that since no transgression between species takes place, CRISPR is equivalent to traditional breeding. This mirrors a sociotechnical imaginary of CRISPR, which was identified among American proponents of using CRISPR in new plant varieties for food (Bain et al., 2020), however our study shows that this also applies to uses of the technology in animals.

CRISPR as a game-changer

Some study participants maintained that even without crossing species, applying CRISPR involves a risk of off-target and unintended changes. These are concerns which are close replicas of what were important themes in public opposition when GM first was introduced (see e.g., Lassen & Jamison, 2006) and which throughout has been a key theme in debates about GM (Frewer, 2017). This suggests that the qualitative difference between GM and genome editing, which is highlighted among proponents, is met with some suspicion among study participants. Thus, an argument that 'Precise edits do not necessarily result in precise outcomes' (Friends of the Earth NGO, as cited in Bain et al., 2020, p. 266) fairly well summarizes what was brought forward also in our interviews. The concern for potential unforeseen and irreversible consequences, which the original GM technology has been met with, also maps into CRISPR. Still, all participants readily engaged in concrete discussions of what was at stake if CRISPR was to be adopted in the salmon industry. A few participants from the salmon industry and the trade union highlighted the positive potentials for the industry, but the larger parts of interviews with both stakeholders and citizens addressed various concerns for potential negative impact of the genome editing technology used in salmon farming. These concerns related, firstly, to negative impacts on ecosystems and the environment, most often articulated with reference to the wild salmon, and, secondly, to the farmed salmon's welfare and dignity. This partly aligns with findings from earlier research on GM and genome editing technologies. Concern for the environment is well established in most research on acceptability of technologies and ranks high on the list of topics being met with opposition from the general public, both in relation to GM and genome editing (Frewer et al., 2004; Kamrath et al., 2019). However, it is noteworthy that the other theme, which ranks highest in research on public concern of GM, namely human health and safety (Kamrath et al., 2019), was hardly brought up in stakeholder or focus group interviews. We interpret this as related to the high trust in the food safety systems in Norway as also suggested by Bugge (2020) and NBAB (2020). Norwegian citizens and stakeholders seem fairly confident that existing regulations ensure health and safety for people.

CRISPR-animals

The concerns for farmed salmon welfare and dignity are noteworthy in two respects. First, it demonstrates that using genome editing technologies on animals give rise to a complex set of challenges relating to their integrity and welfare. Animals are protected through animal welfare laws such as the Norwegian Animal Welfare Act (Ministry of Agriculture and Food, 2009). However, genome editing raises questions of animals' intrinsic value. While intrinsic value is included in the Norwegian Act, it is not clear how this should be operationalised in practice. Therefore, genome editing of animals sharpens the need to develop our understanding of what integrity and welfare is for different species which we breed. In the cases brought up in the interviews, participants' reasonings about these questions were highly context-dependent, adding specific conditions for use. This underlines the difficulty in abstracting normative principles which can be applied to other animals in other contexts and suggests that further research into this topic needs to proceed on a case-by-case basis.

Furthermore, fish are often considered a border-animal in the sense that they are often not categorized with other animals and tend to escape our moral concern (Winther & Myskja, 2022). However, the results show that many do in fact have concerns about the life and wellbeing of salmon, both farmed and wild. Salmon was domesticated as recently as the 1970s in Norway, and unlike other domesticated production animals, the farmed salmon's wild cousin is still around. This invites for comparison between the two. The wild salmon being described as an iconic species to which we have a responsibility to ensure an undisturbed natural habitat, while the farmed salmon is usually described in less appreciative or even derogatory terms. Even so, it is noteworthy that many participants held that such animals also have an integrity we are required to respect. The main concern is related to how genome editing potentially can affect the well-being of the fish. Several study participants stressed that farmed salmon must be allowed to live as naturally as possible. At the same time, the nature of salmon farming was frequently emphasised as a challenge for this requirement, regardless of any implementation of genome editing. In this context, 'welfare' is understood as not merely indicating the absence of diseases and overall health but rather indicates quality of life. This concern for welfare lends support to claims that perception of fish is changing and that they are increasingly being recognized as animals with intelligence, sociality, and ability to feel pain (Lien, 2015; Medaas et al., 2021, p. 29).

Some research has been done on public attitudes to GM of salmon in the past: A mixed-method article from 2010 found that a GM salmon was mostly negatively received, with concerns about possible negative environmental impact and a rejection of using the technology to stimulate growth (Grunert et al., 2001, p. 12-14). Another study found that consumers are willing to pay more for non-GM salmon in order to avoid its GM-counterpart (Chern et al., 2002). But these results are dated, and there is a need to investigate whether the transition to CRISPR causes any changes in such perceptions.

Moral position or pragmatic deliberation?

In research about public acceptance of GM technologies, moral objections about naturalness are often cited as grounds for rejection, but there appears to be some disagreement as to the significance of it. Thematically, moral concerns address conflicts with religious (violation of divine order) and other fundamental values, such as protection of the order of nature, sometimes articulated as a concern for 'naturalness' (Lassen et al., 2002; Lassen & Jamison, 2006; Scott et al., 2018). In qualitative as well as some survey studies, moral values are found to be more important than other causes of concern which relate to negative views on gene technologies (Frewer et al., 2004). Scott et al. (2018) argue that morally based opposition is treated as an absolute, exempt from consequence-based trade-offs, and evoking strong negative emotions, such as anger, contempt, and disgust. Evidence that information about risk and benefits does little to persuade about acceptability of genome edited foods supports this view (Scott et al., 2018). This position questions the rationale of the research on public attitudes to gene technologies which focuses on rational predictors of opposition, such as weighing benefits against costs and risks (Bruce, 2017; Kamrath et al., 2019).

While, in the present study, hardly any reference to religious principles was presented, ideas of nature as a self-organising system which should not be tampered with seemed to underlie the uneasiness about the uncertainty and unpredictability of using CRISPR. However, it was an overarching characteristic that study participants reflected pragmatically about specific costs and benefits associated with using genome editing in salmon farming. Even some who expressed a strong morally-based opposition did not insist on rejecting the technology altogether, but appeared to accept that specific weighing of risks and benefits of CRISPR was unavoidable.

There are several explanations for this pragmatism. It may be reserved for CRISPR because of its less invasive character leading to a view on potential risks as less threatening. It may also be based on the time that has passed since GM technologies were originally introduced, making them more familiar to people, and thus less threatening. Finally, it may be caused by most participants acknowledging that the salmon farming industry is here to stay, and some are willing to accept some trade-offs to preserve the environment and the wild salmon populations. No firm conclusion can be drawn based on our data, but the fact that crossing of species raised more severe opposition in the interviews suggest that the pragmatic approach is reserved for CRISPR.

Still, it should be maintained that the interviews highlight strong views which appears to be based on very firm moral principles. Firstly, as described above, protection of wild salmon was a firm and consensual position that needed no argument or explanation. Secondly, for many participants it was obvious that benefits to the industry alone were no legitimate reason to adopt CRISPR in salmon farming. While some stakeholders from the industry highlighted the great potential for improving productivity and resource utilization, most stakeholders and citizens maintained that this would not be legitimate and sufficient aims for introducing CRISPR. Instead, it was frequently highlighted that genome editing should neither be used to increase the industry's profits, to obscure negative consequences of the industry, nor to treat symptoms instead of solving underlying problems. Similar views have been found in earlier studies (Bugge, 2020; Lassen et al., 2002; Rose et al., 2020), and such views may reflect a general critique of modern agriculture and aquaculture industries (Lucht 2015). This critique was also evident in the worries expressed in our interviews, that solving problems for the salmon industry would further the industry's expansion and thereby create even more problems. On the other hand, as argued by Frewer (2017), not all technologies to be used in agriculture are rejected, and similarly in the interviews not all uses of CRISPR were rejected. The critical views on the salmon industry's potential aims and gains seems to express a strong view that genome editing should be accepted only when seeking to obtain aims which are for the good of the environment, the wild salmon, or for the health and wellbeing of the farmed salmon. This is in line with earlier research which found that citizens maintain that genetic technologies should only be used to promote societal goods, not individual benefits (Bugge, 2020; Gatica-Arias et al., 2019; Lassen et al., 2002; NBAB, 2020; Yunes et al., 2021).

Regulation

There are ongoing debates in several countries about whether genome-edited organisms should be exempted from GMO legislation. Proponents of the technology see GM regulation as hindering technological revolution and decreasing immediate commercial value of CRISPR because of lengthy approval processes (Gupta et al., 2021; Hallerman et al., 2022; Hallerman & Graubau. 2016; Niraula & Fondong, 2021; Singh & Bokolia, 2021). The argument that CRISPR generates organisms which are similar to conventionally bred organisms, and that products of the technology therefore are to be seen as ordinary products are arguments in favor of not including CRISPR in GM regulation. While some results from our study suggest that CRISPR may be met with less opposition and concern than the original GM technology, and therefore in the end be seen as qualitatively different from it, there are other results pointing in the opposite direction. In fact, there is among citizens as well as some experts still doubt that CRISPR technology delivers on the promise of being sufficiently precise and safe. This suggests that CRISPR technology still needs specific regulatory assessments.

Limitations of the study

The interviews were conducted during Covid-19 and had to be done by virtual platforms instead of in person. This offered benefits in terms of cost effectiveness, as costs for travel and rooms for focus groups were repealed and made it easier to include participants from different areas of Norway in the same group. On the other hand, it made interaction among participants in the focus groups difficult, which resulted in less spontaneity and openness. It is likely that more variation in views and more personal experience could have been expressed, had the participants met in person. It may also have made it difficult to establish trust in the stakeholder interviews, which is relevant, since salmon farming touches upon sensitive topics.

We found it difficult to interview both stakeholders and citizens who had no prior interest or knowledge about genome editing, and especially when it came to moral implications of the differences between GM and genome editing technologies. When explaining how CRISPR is different from GM we found it difficult to avoid invoking laden terms such as ‘more efficient’, ‘more targeted’, and ‘less invasive’. Such explanations obviously introduce a potential positive bias in how some participants come to perceive the technology. Still, critical views on gene technologies were ample in the data, and in most focus groups there was one or several participants voicing such views.

Conclusion and perspectives

Some uses of CRISPR, notably for environmental and animal welfare improvements, are seen as potentially acceptable in situations where no other solutions are at hand and the effects are exclusively positive. However, the promises of how CRISPR can solve problems for the salmon industry are met with some suspicion, sometimes seen only as symptom treatment, and sometimes as promoting further expansion of the salmon farming industry, which is a prospect which divides.

Genome editing of animals raises questions about animals' intrinsic value. First, the meaning of this concept is open for various interpretations. Second, our data suggest that the meaning of the concept depends on the animal in question, differences between farmed and wild salmon being one example. Further research on this is warranted.

It is unclear whether CRISPR can be an ethical game-changer. Concerns which met the original GM technology are still present in discussions about CRISPR, and while the positive potentials of the technology are acknowledged to some degree, morally based opposition along with social critique should be expected. Moral and pragmatic considerations highlighted in this study were all context specific. This underlines the need for research and regulation to proceed on a case-by-case basis.

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