EXTRAPOLATION OF EXISTING CODEX VETERINARY DRUG MRLs FOR AQUACULTURE

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Definitions / Abbreviations

The present definitions are extracted from:

- *The glossary of terms established by CCRVDF (CXA 5-1993).*
- *Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food - A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization - Annex 1 Glossary of Terms.*
- *EU regulation.*

1. **Reference species:** is used to refer to a species in which MRLs have been established based on a scientific evaluation by JECFA
2. **Concerned species** is used to refer to a species for which extrapolation is being considered
3. **CCRVDF**: Codex Committee on Residues of Veterinary Drugs in Food
4. **JECFA**: FAO/WHO Join Expert Committee on Food Additives, also tasked with expert advice related to veterinary drug residues.
5. **Related species:** means species belonging to the same category of food-producing species of ruminant and non-ruminant mammals (includes pigs, horses, and rabbits), birds, or bony fish (Osteichthyes).
6. **Unrelated species:** is used to refer to species belonging to different categories of food-producing species.
7. **Major species**: means cattle, sheep for meat, pigs, chicken including eggs, and Salmonidae (COMMISSION REGULATION (EU) 2017/880)
8. **Minor species:** means any species other than major species (COMMISSION REGULATION (EU) 2017/880)
9. **M: T (the marker 'M' to total residues of toxicological concern 'T')**
10. **The marker residue**: EHC 240 defines it as the parent drug, any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels.

    CXA 5-1993: A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk, or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.
11. **Total residue** CXA 5-1993: the total residue of a drug in animal-derived food consists of the parent drug together with all the metabolites and drug-based products in the food after administration of the drug to food-producing animals. The number of total residues is generally determined by means of a study using the radiolabeled drug and is expressed as the parent drug equivalent in mg/kg of the food.
12. **Maximum Residue Limit for Veterinary Drugs** (MRLVD): Is the maximum concentration of residue resulting from the use of a veterinary drug that is recommended by

the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also considers other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.

13. **Residues of Veterinary Drugs**: Include the parent compounds and/or their metabolites in any edible portion of the animal product and include residues of associated impurities of the veterinary drug concerned.
14. **Veterinary Drug**: Any substance applied or administered to any food-producing animal, such as meat or milk producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic, or diagnostic purposes, or for modification of physiological functions or behaviour.
15. **Withdrawal Time (period) and Withholding Time**: The interval between the time of the last administration of a veterinary drug and the time when the animal can be safely slaughtered for food or when milk or eggs can be safely consumed (EHC 240).
16. **EHC 240**: A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization related to the Principles for Risk Assessment of Chemicals in Food.
17. **EWG:** Electronic working group
18. **VICH**: The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. The VICH have prepared four guidelines to facilitate the mutual acceptance of metabolism and residue depletion data for veterinary drugs used in food-producing animals by national/regional regulators. VICH has developed a draft guideline (draft VICH-GL 57) for residue depletion study in aquatic species.
19. **NENA Region:** the Near East and North Africa Region
20. **MENA region**: The Middle East and North Africa region. The terminologies MENA, NENA and Arab region are being used interchangeably in this document, although they may refer to different countries
21. **The Arab region:** countries members of the League of Arab States, having Arabic as their official language.

Abstract / Keywords

This study aims to explore the application of the guidelines on extrapolation of MRLs developed and adopted by the Codex Committee on Veterinary Drugs in Food (CCRVDF) for the development of MRLs relevant to aquaculture species in the Arab Region / Middle East and North Africa Region (MENA).

An attempt is made to address current and future needs of the aquaculture industry in the Arab region, to avail itself with the guidance required on MRLs for veterinary applications, in species not covered by Codex standards.

To this end, the status and future developments of the aquaculture industry were reviewed, along with the guidance offered by Codex, as well as other scientific research, available data and reports published by international agencies – such as FAO, the Word Bank – and also expert bodies such as JECFA.

This study concluded that the MRL extrapolation approach established by Codex was applicable to develop MRLs for veterinary substances possibly used in the production of aquaculture finfish and which were identified as a priority by countries farming different finfish species.

The developed methodology was therefore applied to derive MRLs for the following compounds: **Deltamethrin, Flumequine, Lufenuron, Teflubenzuron, Emamectin Benzoate and Diflubenzuron** in finfish species of interest for the MENA region.

This resulted in attributing MRLs for the substances identified above that are applicable to Tilapia, Seabass and Seabream, which are amongst the most cultured finfish species in the MENA region, thus offering direct support to addressing the gaps in the regulatory requirements of the aquaculture industry in the MENA region.

Keywords:

Aquaculture; Finfish; Veterinary drugs; MRLs extrapolation; CCRVDF principles of extrapolation.

Structure of the Study

The purpose of the study

To apply the CCRVDF guidelines on extrapolation of MRLs for the development of MRLs relevant for veterinary drugs used by the finfish aquaculture sector in the MENA region. This approach will offer an evidence-based approach for the adoption of such MRLs, hence ensuring food safety and supporting fair trade of aquaculture products from the region.

Context and challenges

The aquaculture sector continues to register great growth given its essential contribution to food security and economic development. This trend is expected to continue according to global forecasts published in the 2020 edition of The State of World Fisheries and Aquaculture which reports on the intensification of this activity, expansion into new areas, development of new technology, and the potential for increased income resulting from this industry worldwide.

It is important that operators of the aquaculture sector rely upon robust guidance such as standards related to MRLs of veterinary drug residues to be followed, when using these substances according to good production practices. This is a condition to support safety of products and access to domestic and international markets.

The application of Codex guidance to derive such MRLs, from Codex standards where applicable, offers opportunities to address some of the gaps in the availability of the needed food safety guidance related to veterinary drug MRLs used in the aquaculture sector, while supporting international convergence of food safety measures stemming from Codex standards.

This is particularly important when the reliance on effective veterinary medicinal products is becoming ever more crucial to prevent and/or treat disease outbreaks that threaten aquatic animal production

The Codex Alimentarius Commission (CAC), with the support of the technical Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), establishes and adopts MRLs for drugs intended for use in different commodities. These standards rely on scientific expert advice provided by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) based on conservative approaches requiring the availability of relevant data and field residue studies. Until now, few MRLs were established by Codex for vet drugs used on fishery products (6 compounds) due notably to the lack of data, the wide range of fish species farmed, and the costly nature of the development of fish residue studies.

The lack of MRLs for fish species might closely affect the development of the aquaculture industry and subsequently lead to the reduced and limited variety of drugs available to fight aquaculture species diseases. The absence of internationally accepted MRLs in the targeted species/tissues may lead to the application of a zero-tolerance approach or obstacles in international trade.

Codex developed an alternative approach, through extrapolation of established MRLs for select fish species to derive other needed MRL values for other species. This approach was documented in Annex C to the Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Foods in the Procedural Manual: "Risk Management Policy applied by CCRVDF for the Extrapolation of MRLs to One or More Animal Species".

The present study will rely on the guidance developed by Codex on extrapolation of MRLs to attempt the development of MRLs for veterinary drugs that may be used with aquaculture finfish species that may be considered as a priority for the MENA region.

The demonstration of applicability of this approach may offer a solution for future applications to address the need for MRLs for more species, for which data are unlikely to be forthcoming but which are considered important for the development of aquaculture in the MENA region.

Key Scientific Sources Reviewed and Relied Upon in the Conduct of this Study:

This study relied upon key guidance documents and other references developed by Codex, its expert bodies and other international organizations:

- Documents and reports of the various sessions of the codex committee on residues of veterinary drugs in food, dedicated to the extrapolation guidelines:
  - REP21/CAC.
  - CX/CAC 21/44/2 Add.2.
  - CX/RVDF 21/25/8.
  - REP21/RVDF.
  - CX/RVDF 18/24/7.
  - REP18/RVDF.
- JECFA reports related to MRLs extrapolation: 78th and 81st meeting.
- Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food.
- Maximum Residue Limits (MRLs) and Risk Management Recommendations (RMRs) for Residues of Veterinary Drugs in Foods (CX/MRL 2-2021).
- Glossary of Terms and Definitions (Residues of Veterinary Drugs in Foods) (CXA 5-1993).
- The review of scientific documentation and expert report on the risk assessment of fish diseases;
- The document of the World Organization for Animal Health (OIE) (2021). OIE Strategy for Aquatic Animal Health 2021 – 2025. OIE, Paris, 32 pp..
- The 2022 FAO document related to aquaculture.

1. Review of Codex (CCRVDF) guidelines on extrapolation of vet drugs MRLs for aquaculture (background, basis, development, application)

1.1 Reliance upon Extrapolation Methodologies by Food Regulatory Jurisdictions to Derive MRLs for Select Chemical Substances in Conjunction with Food Production – Background

Various scientific committees and regulatory authorities have investigated and adopted methodologies based on extrapolation to derive MRLs for chemical substances used in conjunction with food production. The basic principles of the approach are included in CODEX guidelines developed by CCPR and CCRVDF as well as in the regulatory principles for the development of MRLs used in certain countries such as Canada, the United States and the European Union.

MRL extrapolation was documented in the guidelines for the risk assessment of chemicals in food (EHC 240), developed in 2009 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). According to these principles, by way of extrapolation, MRLs adopted for substances in one or more species could be extended to a related species provided that the metabolic profile is comparable, the marker residue is present in the species for which the extensions are considered at sufficient levels for monitoring by validated analytical methods and there is an approved use.

The methodology of extrapolation has already been adopted by some regulatory jurisdictions such as the European Union (EU) since 2009, in accordance with Regulation ((EC) No 470/2009 of the European Parliament and of the Council, Commission Regulation (EU) 2017/880 of 23 May 2017).

In this context, guidelines on safety and residue data requirements for the establishment of Maximum Residue Limits in minor species were developed:

- guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00),
- Safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005).
- CVMP guidelines on data requirements for veterinary medicinal products intended for minor uses or minor species, and Technical Guidance: Extrapolation of data from major species to minor species regarding the assessment of additives for use in animal nutrition (EFSA 2008 (The EFSA Journal, 803: 1-5).

The US Food and Drug Administration (US FDA) adopted the extrapolation approach on a case-by-case basis. Flexibility was provided to the Center for Veterinary Medicine to derive MRLs through extrapolation where scientifically appropriate from a major species to a minor species (Code of Federal Regulations Title 21).

Considering the extensive list of compounds in the database on countries' needs for MRLs, both JECFA and JMPR considered the extrapolation methodology to address challenges related to the lack of data and limited submissions for certain substances and species.

Generally, the approach followed consists of the extension of available data from one or several representative commodities to related commodities in the same commodity group or subgroup for which studies have not been conducted. Then, MRLs are proposed by using the extrapolation approach according to principles established in this regard.

1.2 Background of CCRVDF investigations related to MRLs extrapolation.

This section will review the CCRVDF discussions that led to the development and adoption of the principles of MRL extrapolation for veterinary drugs.

Key points:

CCRVDF has considered the development of guidance on MRL extrapolation since its 19th session in 2010. Several meetings were devoted to discussing the principles, challenges, and possible limitations of the methodology.

The option of extrapolation of MRLs from a species in which a full residue data package has been evaluated to other species was considered, with the application of risk analysis as a foundation for the decision-making process.

Several working groups were established by the committee notably to ***collate and summarise all the available national and regional guidelines and documents and published literature pertinent to the extrapolation of MRLs, propose potential risk analysis policy for use by CCRVDF when considering extrapolating MRLs and prepare a list of substances with existing MRLs in several species/food matrices for which extrapolation is considered necessary and make a proposal for prioritization.*** *In light of the EWG discussions, proposals, principles, and criteria were developed for the application of extrapolation as a methodology for the establishment of veterinary drug MRLs, notably for finfish.*

The Committee recommendations were adopted by CAC44 as a methodology to develop MRLs for veterinary drugs and was introduced into the procedural manual (risk analysis principles applied by the codex committee on residues of veterinary drugs in foods (section 3.4 - evaluation of risk management options).

The application of the methodology for finfish was considered by the 22nd session of CCRVDF and two MRLs ***concerning Deltamethrin and flumequine*** *were proposed by the EWG according to the extrapolation methodology to be discussed in the upcoming session of the committee in February 2023 (CCRVDF26).*

2. Review of codex MRLs used in aquaculture products not relevant for the Arab region but with potential to support guidance for aquaculture products farmed in the region.

So far, JECFA has established MRLs only for **9 veterinary drugs** for finfish that have been adopted by CAC. These substances have been evaluated by JECFA based on data provided only for three species of finfish and crustaceans (Salmon, Black tiger shrimp, and Trout).

The details related to the MRL's vet drugs are presented in the following table:

Table1: List of MRLs established by JECFA for finfish

Nb	Vet drug	Activity	Reference species	MRLs (µg/kg)	Adoption
01	Diflubenzuron	Insecticide	Salmon (muscle plus skin in Natural proportions)	10	CAC44 (2021)
02	Teflubenzuron	Insecticide	Salmon (muscle and fillet)	400	CAC40 (2017)
03	Lufenuron	Insecticide	Salmon and trout (muscle and filet)	1350	CAC41 (2018)
04	Amoxicillin	Antimicrobial agent	Finfish (muscle and fillet)	50	CAC41 (2018)
05	Ampicillin	Antimicrobial agent	Finfish (muscle and fillet)	50	CAC41 (2018)
06	Flumequine	Antimicrobial agent	Trout (muscle)	500	CAC28 (2005)
07	Oxytetracycline	Antimicrobial agent	Fish (muscle)	200	CAC26 (2003)
08	Emamectin benzoate	Antiparasitic agent	Salmon and trout (muscle and filet)	100	CAC38 (2015)
09	Deltamethrin	Insecticide	Salmon	30	CAC 26(2003)

3. Review current and future aquaculture industry needs in the arab region

Key points:

In the Arab region, the aquaculture sector is still underdeveloped compared to other regions. There is, however, good potential for further growth of aquaculture production in the region with national strategies being developed and implemented in some Arab countries to enhance the development of the sector. Several possible risk factors are to be considered including notably climate change, infectious diseases and limited access to safe and effective veterinary substances.

The aquaculture production consists almost entirely of finfish, represented by the common carp, Nile tilapia and silver carp as the main cultured species.

3.1 Introduction

Global production of aquaculture animals, including fish, crustaceans, molluscs and other aquatic animals is estimated at 87.5 million tonnes in 2020 (FAO, 2022), representing 49 percent of aquatic animal production. Asian countries accounted for 70 percent of the production followed by countries in the Americas, Europe, Africa, and Oceania. African countries account for the lowest rate representing only 2.57% of total world's production (2.2 million tonnes), essentially for finfish (1.857 million tonnes), dominated by Egypt, which is considered as Africa's major aquaculture producer. Additionally, aquatic foods remain the most traded food commodities in the world with a total of around 60 million tonnes recorded for global exports in 2020, worth USD 151 billion[1].

To support the growth and development of the aquaculture sector, the global vision for aquatic animal health was recently proposed in the document entitled "OIE Strategy for Aquatic Animal Health 2021–2025" (OIE, 2021). Implementation of this strategy will improve the health and welfare of aquatic animals worldwide, thereby contributing to sustainable economic growth, poverty reduction and food security, which will help achieve five UN Sustainable Development Goals (OIE, 2021).

In the Arab region, aquaculture has been impacted by climate change, conflict, and the COVID-19 pandemic suggesting that effective resilience planning is needed. Management of the sector varies across the region and needs to be reviewed to ensure that regulatory frameworks are robust and effective enough to support the development of the sector as well as the level of investment and interest provided from high level economic development ministries and oversight bodies.

Aquaculture production was worth USD 2.3 billion in 2018 in the Arab region, two-thirds of which came from Egypt and around one-quarter from Saudi Arabia. Production has been growing steadily since the 1980s, more than doubling over the last ten years and increasing by 50 percent over the five years preceding 2018 to reach 1.7 million tonnes.

Although current aquaculture production levels are low, countries of the Arab region have high potential and ambitions to further develop the sector, often for improved food self-sufficiency.

3.2 Aquaculture production in Arab Countries

In the Arab region, aquaculture production consists almost entirely of finfish, with the common carp, **Nile tilapia** and silver carp as the main cultured species. Shrimp farming has thrived only

in Saudi Arabia along the eastern shores of the Red Sea in the last few years. In Egypt, shrimp culture has been attempted and common carp culture is carried out in rice fields. The culture of marine finfish is conducted mostly in intensive culture systems such as near shore cages and, to a lesser extent, in coastal raceways and brackish water lagoons.

Aquaculture production continues to grow well above global rates and there is good potential for expansion not only in Egypt but also in most other Arab states where extensive research and development of marine culture is underway and where production is well below its potential (Table 4).

Table 2: Aquaculture production in the MENA region in 2018 (FAO, 2022)

Country	Aquaculture production (tonnes) (2018)
Algeria	5 100
Bahrain	0
Egypt	1 561 457
Iraq	25 737
Jordan	900
Kuwait	198
Lebanon	1 031
Libya	10
Mauritania	-
Morocco	1 267
Oman	451
Palestine	749
Qatar	10
Saudi Arabia	72 000
Sudan	1 980
Syrian Arab Republic	2 350
Tunisia	21 826
United Arab Emirates	3 350
Yemen	0
NENA region	1 696 436

3.3 List of major fish species involved with aquaculture in Arab region

Over 70 aquatic animal species, including finfish, crustaceans and molluscs are farmed in MENA region, for commercial purposes as well as research. Currently, aquaculture is restricted to about 45 species and is dominated by finfish, which represents 97 percent of total aquaculture production in 2014 (Table 5 and Figure 1). Nile tilapia (*Oreochromis niloticus*) has by far been the most important farmed finfish during 2005–2014 with an average annual growth of 16.3 percent. Nile tilapia alone contributed 50 percent to total MENA's aquaculture output in 2014, followed by cyprinids (common carp, silver carp, grass carp and bighead carp), which

contributed 26 percent. Farming of marine species, including mullets (flathead grey and thinlip mullet), gilthead seabream and European seabass, in brackish water and seawater environment is also widely practiced. Rainbow trout is the only temperate fish species grown in the MENA region, mainly in the Lebanon with smaller volumes in Morocco (FAO, 2016)

Table 3: List of major fish species involved with aquaculture in MENA region (FAO, 2016)

Common name	Production (tonnes) 2014
Nile tilapia	768 271
Cyprinids nei	153 629
Rainbow trout	127 715
Common carp	125 787
Mullets	119 647
Silver carp	85 439
Whiteleg shrimp	35 465
Gilthead seabream	27 869
European seabass	17 449
Grass carp	17 307
Bighead carp	17 034

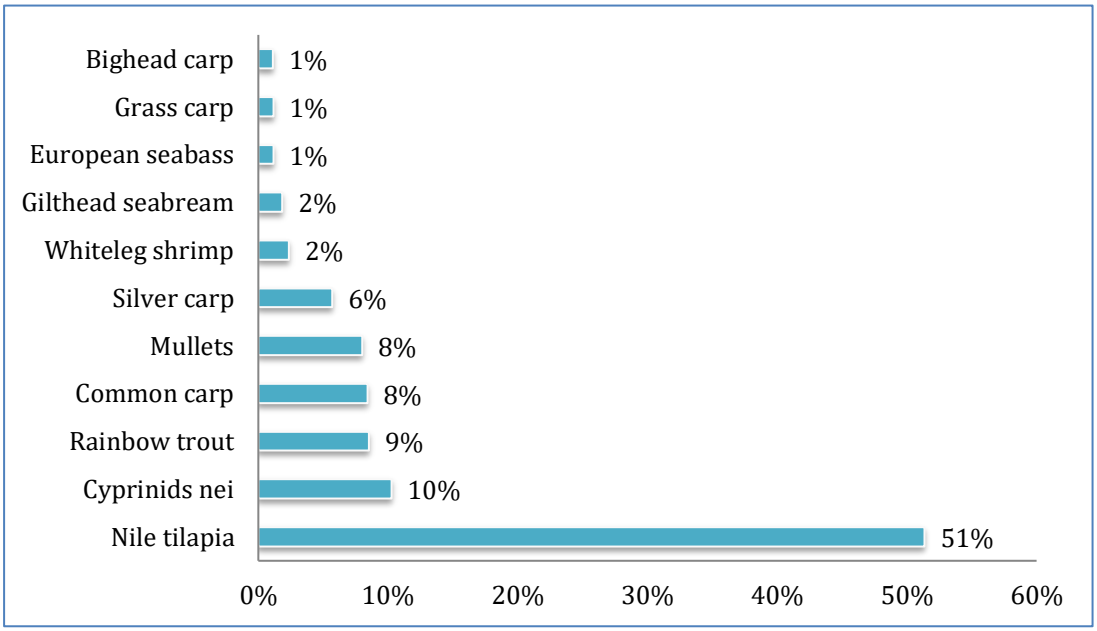


Figure1: Major fish species involved with aquaculture in MENA region

A total of 43 species of finfish, shellfish, and aquatic plants were farmed in the region (FAO, 2022). Tilapia (mainly *Oreochromis niloticus*) was produced in the 15 following countries of the MENA region: Algeria, Djibouti, Egypt, Palestine, Iraq, Jordan, Lebanon, Morocco, Oman, Somalia, Sudan, Syria, Tunisia, Turkey, and Yemen) and represented 63 percent of total 2018 production, followed by mullets (14 percent) and carps (12 percent). Marine finfish (gilthead seabream, European seabass, and meagre) represented around six percent of total production (FAO, 2022).

The capacity to grow tropical marine finfish such as grouper, amberjack, and yellowtail is increasing in all the Gulf countries, but the quantities remain limited, while Asian seabass was mainly produced in Saudi Arabia and the United Arab Emirates.

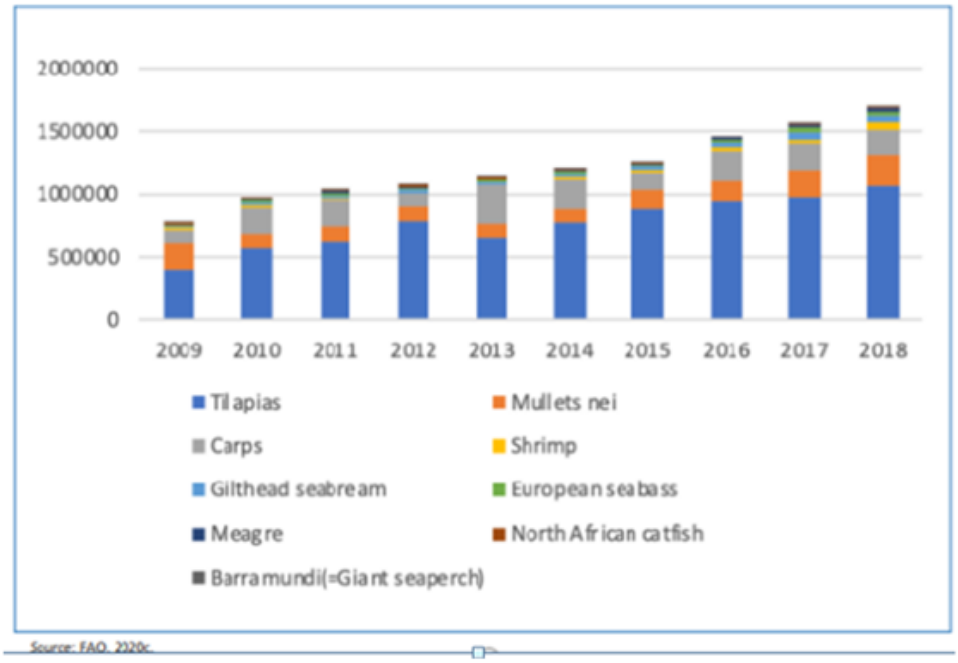


Figure 2: Production of major farmed species groups in the MENA region (2009-2018) (FAO, 2022)

Traditionally, aquaculture research has been the strongest in Egypt, Kuwait, Morocco, Saudi Arabia, and Tunisia, although Algeria, Bahrain, Oman, Qatar, and the United Arab Emirates have also built significant capacity. In Lebanon, the Aquaculture and Aquatic Science Centre at the American University of Beirut has also been active in developing the sector over the years.

Mediterranean aquaculture can diversify by a slight increase in the number of farmed species. The main species will remain the same, with sea bass and gilthead sea bream dominating the Mediterranean aquaculture in both northern and southern countries. Most of the stakeholders consider that intensive shore cage and flow through land-based tank finfish farms will be partly replaced by an offshore farming system.

Egyptian fish farms accounted for 92 percent of production of the region. This means that the regional statistics are heavily influenced by what happens in Egypt, where pond-based

aquaculture of tilapia and mullet has demonstrated consistent growth since the 1980s. Saudi Arabia accounts for 4.2 percent of the region aquaculture while other significant producers including Iraq (25.737 tonnes), Tunisia (21.826 tonnes), Algeria (5.100 tonnes), Morocco (1.200 tonnes), the United Arab Emirates (3.350 tonnes), and the Syrian Arab Republic (2.350 tonnes).

In Morocco, the aquaculture sector is still underdeveloped compared to other Mediterranean countries. This situation contrasts with the country's production potential estimated at 380,000 tonnes (National Agency for the Development of Aquaculture, 2018). Today, the Moroccan aquaculture sector has more than twenty active aquaculture farms including 16 involving oyster farming, 3 mussel farming, 1 peneculture (clams), 2 fish farming (Sea bass, sea bream and lean) and 1 seaweed farming (ANDA, 2019). Sea bream and sea bass are the fish products targeted by the Moroccan aquaculture strategy. The highest rate of development is expected for the two most ecologically sustainable farming systems: integrated multi-trophic aquaculture and recirculation systems. There is also a growing interest in conservative aquaculture and restocking activities that are not really developed at the regional level until now.

3.4 Obstacles hindering the growth of aquaculture in the MENA region:

The aquaculture sector can be impacted by several risk factors and obstacles summarized below:

- Fish feed: one of the most important obstacles hindering sustainable aquaculture development is production and availability of high-quality feed, sourced at reasonable costs,
- "Fish seed": this is challenge for both availability and price. Two main sources for seed are available through hatcheries or wild catch. The problem of seed price and accessibility usually affects mariculture more than freshwater aquaculture.
- Land and water availability: the scarcity of land and water resources designated for aquaculture activities is another challenge for the region (Eltholth M. and al., 2015)
- Lack of technical training for aquaculture personnel: fish farmers don't usually receive specialized or updated technical training for their best practices to maximize yield and profits from the farm (Dickson, M. and al., 2016).
- The impact of infectious diseases and limited access to safe and effective chemical substances, including veterinary drugs, considered as approved substances when required.

3.5 Potential for further growth of aquaculture production in the region

There is a good potential for further growth of the aquaculture production in the Arab region through the expansion of intensive farming and integrated aquaculture, especially desert areas, where limited resource competition would be observed with agriculture and urban development projects. In addition to the added value of water conservation, this provides maximum utilization of resources using recirculating aquaculture systems (RAS) to overcome the problem of water limitation.

For the development of aquaculture sector in the MENA Region many measures could be implemented notably through:

- The application of recent technologies in fish feed production, especially extruded feed, with an emphasis on good quality feed components and high protein percentages necessary for intensification and species-specific feed.
- Introducing recent technologies in hatcheries management in order to have good quality fish and shrimp seeds at reasonable costs.
- The establishment of a regular system for monitoring and assessing fish tissues to be free from diseases, drug residues, and toxic contaminants, for the sake of public health and to open new markets for the export of fish and fish products.
- The adoption of Biosecurity measures in fish farms with strategies to prevent and control disease incidence through vaccination, medications, and genetic selection of disease-resistant breeds.
- Intensive technical training for workers in the field of aquaculture aimed at achieving the best management practice (BMP), especially in the fish feed mills and hatcheries.

3.6 Fish species of interest in the Arab countries

It is important to identify the main important fish species of interest for the Arab region for which the application of the MRL extrapolation approach would offer a response to enable the safe use of veterinary substances by aquaculture sector in the region.

The methodological approach adopted to define the fish species of interest consists of the following steps:

- To review the list of most cultured species in the Arab region, using country data
- Two criteria for selection will be established:
  - Production levels based on FAO data (FAO, 2022)with scores assigned as follows:
    - Scoring rate 4: high production > 200 000 tonnes
    - Scoring rate 3: medium production [100 000-200 000] tonnes
    - Scoring rate 2: low production [10 000-100 000] tonnes
    - Scoring rate 1: very low production< 10 000 tonnes
  - Frequency of cultivation, in the Arab countries with a scoring system based on the following rating:
    - Scoring rate 4: High Frequency > 4
    - Scoring rate 3: Medium Frequency =3
    - Scoring rate 2: Low Frequency =2
    - Scoring rate 1: very Low Frequency =< 1

The product of two scores will help establish a ranking of priority aquaculture fish species in the Arab region.

The application of this methodology led to establish a list of fish species most cultured in the Arab region in Table 4

Table 4: overview of most cultured fish species in Arab countries

Country	Aquaculture production 2018 (tonnes)	% of aquaculture production in MENA Region	Most cultured fish species
Algeria	5 100	0,252%	▪ Nile tilapia (*Oreochromis niloticus*) ▪ European seabass (*Dicentrarchus labrax*) ▪ Gilthead seabream (*Sparus aurata*) ▪ Meagre (*Argyrosomus regius*)
Bahrain	14	0,001%	▪ Rabbit fish (Safee) (*Siganus canaliculatus*) ▪ Sobaity bream (Sobaity) (*Sparidentex hasta*) ▪ Orange-spotted grouper (Hamour) (*Epinephelus coioides*) ▪ Gilthead seabream (*Sparus aurata*) ▪ Mangrove snapper (Sheggar) (*Lutjanus argentimaculatus*) ▪ Cobia (*Rachycentron canadum*)
Egypt	1561457	77,136%	▪ Nile tilapia (*Oreochromis niloticus*) ▪ Blue tilapia (*Oreochromis aureus*) ▪ North African Catfish (*Clarias gariepinus*) ▪ Flathead grey mullet (*Mugil cephalus*) ▪ Thinlip mullet (*Liza ramada*) ▪ Bluespot mullet (*Valamugil seheli*) ▪ European seabass (*Dicentrarchus labrax*) ▪ Gilthead seabream (*Sparus aurata*) ▪ Meagre (*Argyrosomus regius*) ▪ Shrimp
Iraq	25 737	1,271%	▪ Common carp (*Cyprinus carpio*) ▪ Grass carp (*Ctenopharyngodon idellus*) ▪ Silver carp (*Hypophthalmichthys molitrix*)
Jordan	900	0,044%	▪ Tilapia species
Kuwait	297	0,000%	▪ Nile tilapia (*Oreochromis niloticus*)
Lebanon	1 031	0,051%	▪ Nile tilapia (*Oreochromis niloticus*)
Libya	10	0,000%	▪ Nile tilapia (*Oreochromis niloticus*) ▪ Tilapia species
Mauritania	No data	No data	▪ No data
Morocco	1 267	0,063%	▪ Gilthead seabream (*Sparus aurata*) ▪ European seabass (*Dicentrarchus labrax*) ▪ Meagre (*Argyrosomus regius*) ▪ Atlantic bluefin tuna (*Thunnus thynnus*)
Oman	451	0,022%	▪ Gilthead seabream (*Sparus aurata*) ▪ European seabass (*Dicentrarchus labrax*) ▪ Yellowfin seabream (*Acanthopagrus latus*) ▪ Orange-spotted grouper (*Epinephelus coioides*)

			▪ Nile tilapia (*Oreochromis niloticus*)
Palestine	240	0,012%	▪ European seabass (*Dicentrarchus labrax*) ▪ Gilthead seabream (*Sparus aurata*) ▪ Striped bass (*Morone saxatilis*) ▪ Carp species ▪ Nile tilapia (*Oreochromis niloticus*)
Qatar	10	0,000%	▪ Nile tilapia (*Oreochromis niloticus*)
Saudi Arabia	72 000	3,557%	▪ Nile tilapia (*Oreochromis niloticus*), ▪ Seabass or barramundi (*Lates calcarifer*) ▪ Gilthead seabream (*Sparus aurata*)
Sudan	10 000	0,494%	▪ Gymnarchus species ▪ Heterotis species ▪ Citharinus species ▪ Hydrocynus species ▪ Clarias species ▪ Nile perch (*Lates niloticus)* ▪ Tilapia species ▪ Labeo species ▪ Alestes species ▪ Distichodus species ▪ Niger barb (*Barbus bynni*), ▪ Bagrus species ▪ Mormyrus species ▪ Schilbeidae family
Syrian Arab Republic	3 000	0,148%	▪ Mullets (*Mugil* spp.) ▪ Parids (*Sparus aurata*, *Diplodus* spp., *Pagellus* spp.) ▪ Groupers and seabass (*Dicentrarchus labrax*) Amberjack or yellowtail (*Seriola dumerilii*) ▪ Tilapia species
Tunisia	21 826	1,078%	▪ European seabass (*Dicentrarchus labrax*) ▪ Gilthead seabream (*Sparus aurata*) ▪ Northern bluefin tuna (*Thunnus thynnus*) ▪ Nile tilapia (*Oreochromis niloticus*)
United ArabEmiratess	788	0,039%	▪ Gilthead seabream (*Sparus aurata*) ▪ Tilapia species ▪ European seabass (*Dicentrarchus labrax*) ▪ Siberian sturgeon (*Acipenser baerii*) ▪ Pearl oysters

Table 5: List of Major Fish Species Involved with Aquaculture in the Arab Region

Common Name	Production (Tonnes) 2014	Countries of production

Nile Tilapia	768 271	Egypt, Saudi Arabia, Tunisia Morocco, Algeria, Palestine, Qatar, Sudan, Oman, Libya, Kuwait, Jordan, Lebanon, Syrian, United Arab Emirates
Cyprinids nei	153 629	Iraq
Rainbow trout	127 715	Jordan
Common carp	125 787	Iraq, Palestine
Mullets	119 647	Syrian, Egypt
Silver carp	85 439	Iraq, Palestine
White leg shrimp	35 465	Saudi Arabia, Egypt
Gilthead seabream	27 869	Tunisia, Algeria, Morocco, Syrian, Saudi Arabia, Palestine, Oman, Egypt Bahrain, United Arab Emirates
European seabass	17 449	Tunisia, Algeria, Morocco, Syrian, Egypt Saudi Arabia, Palestine, Oman,
Grass carp	17 307	Iraq, Palestine
Bighead carp	17 034	Iraq

Combining the scoring rate of the two criteria described above leads to establish the following scores for aquaculture fish species in the Arab region as represented in Table 6

Table 6: Scoring rate of aquaculture fish species in the Arab region

Common Name	Production level		Frequency level		Total (frequency score * production score)
	Tonnes	Scoring	Countries	Scoring	
Nile Tilapia	768 271	4	Egypt, Saudi Arabia, Tunisia Morocco, Algeria, Palestine, Qatar, Sudan, Oman, Libya, Kuwait, Jordan, Lebanon, Syrian, United Arab Emirates	4	16
Cyprinids nei	153 629	3	Iraq	1	3
Rainbow trout	127 715	3	Jordan	1	3
Common carp	125 787	3	Iraq, Palestine	2	6
Mullets	119 647	3	Syrian, Egypt	2	6
Silver carp	85 439	2	Iraq, Palestine	2	4
Shrimp	35 465	2	Saudi Arabia, Egypt	2	4
Gilthead seabream	27 869	2	Tunisia; Algeria, Morocco, Syrian, Saudi Arabia, Palestine, Oman, Egypt Bahrain, United Arab Emirates	4	8

European seabass	17 449	2	Tunisia, Algeria, Morocco, Syrian, Egypt Saudi Arabia, Palestine, Oman,	4	8
Grass carp	17 307	2	Iraq, Palestine	2	4
Bighead carp	17 034	2	Iraq	1	2

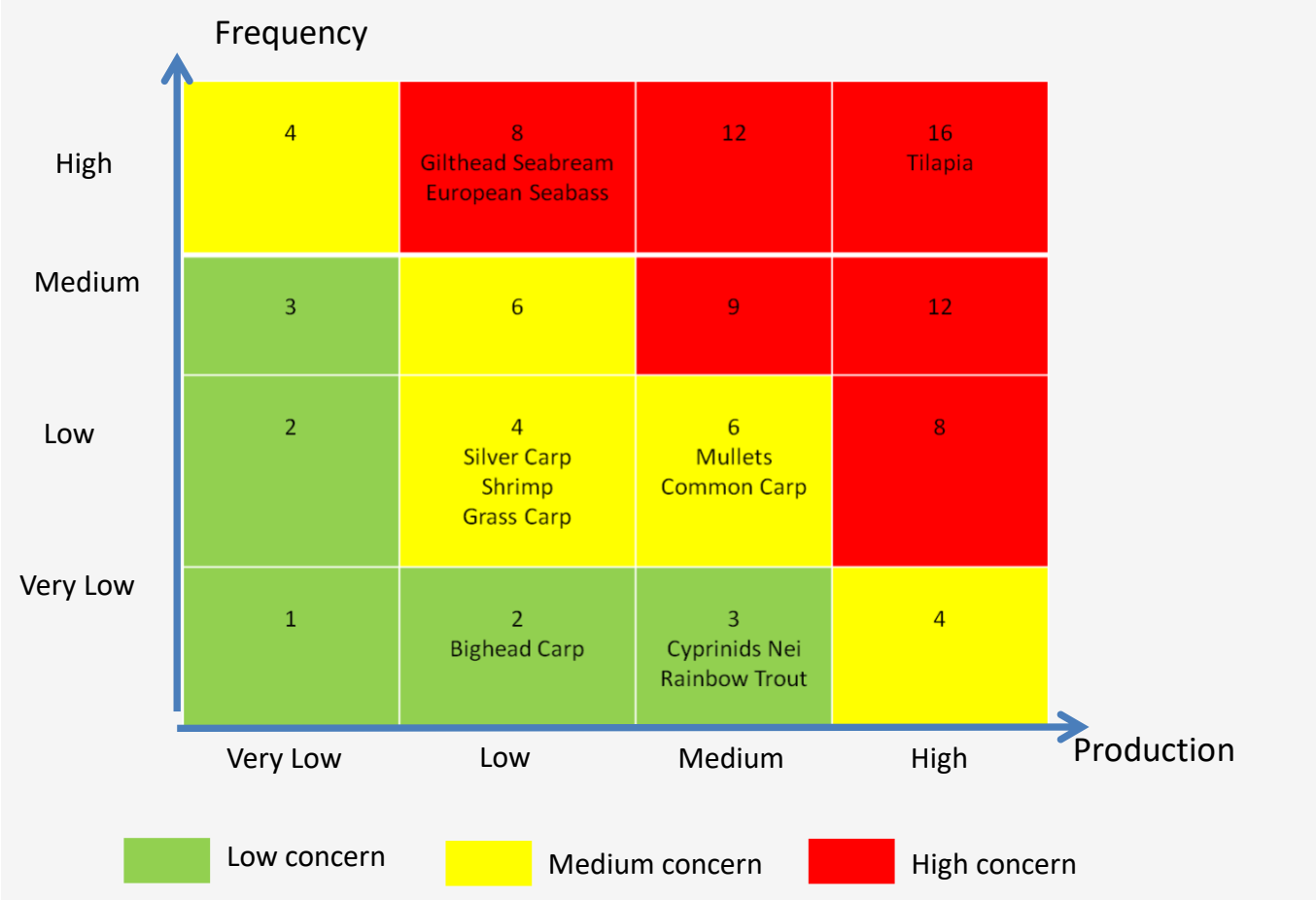


Figure 3: Fish species most cultivated in the Arab countries

***Conclusion**:*

According to the decision matrix established, Tilapia is identified as the fish species most cultivated for aquaculture in the Arab region, followed by Sea Bream and Sea Bass. These three (3) species will therefore be considered as the species of focus for the Arab region, to support safe and effective treatment with the relevant veterinary substances.

3.7 The potential of the fish species diversification for the development of aquaculture in the Arab region

The number of fish species used in the Arab region for aquaculture is limited compared to other countries; only 11 species are cultured in the region (table 7).

With the growing concerns over climate change, disease outbreaks, market fluctuations and other uncertainties, it is important to consider species diversification in aquaculture practices (Harvey B. and al., 2016)

Moreover, such diversification may contribute to sustainable aquaculture development in the Arab Region. It adds additional benefits by offering new products in the market and reduction of pressure on the wild catch, supported with the utilization of diverse natural resources, farming environments, or farming systems and technologies. Therefore, increased aquaculture production should be associated with high species diversity.

4. Needs for veterinary drug MRLs supporting the aquaculture sector in the Arab region

4.1 Impact of infectious diseases in aquaculture

Husbandry practices used in aquaculture increase the vulnerability of farmed fish to diseases due to external factors like a higher density production system, the perturbations in ecological system balances related notably to pollution and climate changes (Moreira M. and al., 2021). Intensification of aquaculture has led to an increasing need of using veterinary drugs to fight against the economic impact of disease outbreaks.

Several studies carried out on fish from aquaculture have shown their vulnerability to developing infections (VAGIANOU and al., 2017; Bull. and al., 2008). Like all husbandry species, aquaculture can be the subject of multiple disease outbreaks linked to infectious agents which are the main constraints in aquaculture production (Barber I. and al., 2007).

Parasites are the most commonly found pathogen; accounting for up to 80% of the total infections in fish on farms (Shaheen H., 2013).

Bacterial infections in fish are also present with a higher incidence of mortalities when compared to parasitic infestations. Infections with *Aeromonas hydrophila, Flavobacterium columnaris, Pseudomonas fluorescens, Yersinia ruckeri, Edwarsiella tarda, Edwardsiella ictaluri, Vibrio* spp. and *Streptococcus* spp. were reported in Egyptian aquaculture farms (Moustafa M. and al., 2010; Abdelsalam M. and al., 2017) (Moustafa, et al., 2010; Abdelsalam et al., 2017).

To a lesser extent, there is an incidence of mycotic infections which are mostly induced by *Saprolegnia* spp., *Ichthyophonus hoferi*, and *Branchiomyces* spp. (Shaheen H., 2013).

A. hydrophila and *Saprolegnia* spp. infections and their co-infection are the most important diseases in fish farms (Shaheen A. and al., 2013).

4.2 Main aquaculture chemicals used in the Arab region

Several sets of chemicals including antibiotics are used at different steps in aquaculture, used notably for pond preparation, animal health management, and water quality management (Bangladesh J. , 2008). But their use must be supported with considerations of safety and efficacy, along with the requirements to manage the possible residues associated with such use.

Current levels of veterinary drugs used in aquaculture worldwide are not easy to determine because different countries have different distribution and registration systems and the amount of vet drugs used in aquaculture differs significantly between countries.

The most used Veterinary drugs in aquaculture by operators of the Arab region are (FAO, 2016):

- The tetracycline family (Oxytetracycline).
- The quinolone family (Flumequine).

Tetracycline is the most likely class of antibiotics to be used in fish farming although they tend to be considered primarily when resistance to quinolones is identified. The latter family of compounds are synthetic molecules with antibiomimetic properties, of which the main antibacterials commonly used in fish farming are oxalinic acid and flumequine (DHAOUADI R. and al., 2015)

Tables 7 offer a summary of the veterinary substances used in the Arab region, along with their mechanism of action and associated indications of use.

Table 7: Main vet drugs used in the Arab region

PHARMACOLOGICALLY ACTIVE SUBSTANCES	
Quinolones	Difloxacin
	Enrofloxacin
	Flumequine
	Oxolonic acid
	Sarafloxacin
Tetracyclines	Chlortetracycline
	Oxytetracycline
	Tetracycline

5. Methodology for the derivation of a pilot set of MRLs, using Codex Guidance

The MRL extrapolation approach adopted by the CCRVDF is intended to be a pragmatic approach for the establishment of MRLs in food producing species for which residue data are not available.

It is based on positive evaluations carried out by JECFA for the reference species and on the respect of extrapolation criteria to have the assurance that the metabolism in the reference species and the concerned species is sufficiently similar to allow the application of MRLs while maintaining the protection of the consumer. The adopted approach is a slightly modified approach from the revised Option C presented at CCRVDF24. It allows the application of the extrapolation methodology from one or more bony fish species directly to all bony fish under determined conditions introduced in Table 11, below. It does not require the intermediate step in which MRLs are first extrapolated to orders of fish based on the groupings presented in VICH GL57. Confirmatory data would still be expected in order to establish adequate withdrawal periods to ensure compliance with extrapolated MRLs.

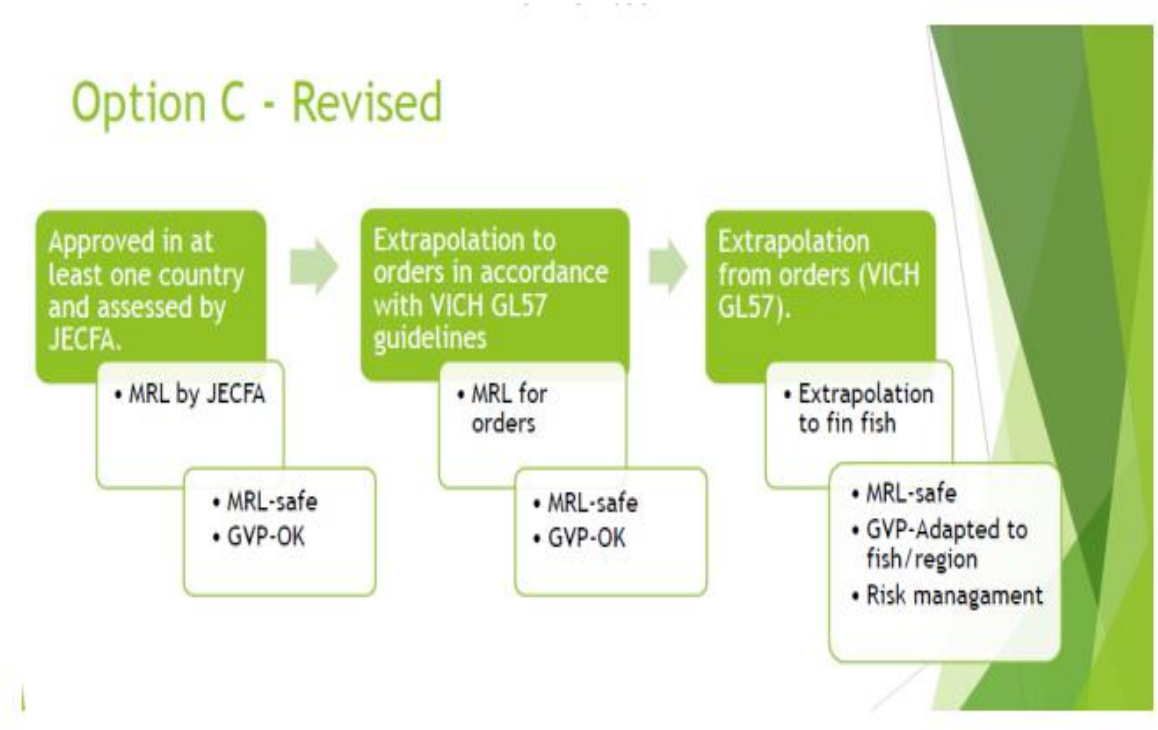


Figure 4: Option C of extrapolation methodology CX/RVDF 21/25/8

Three distinct classes of fish are usually identified: (i) jawless fish (*Agnatha*), (ii) cartilaginous fish (*Chondrichytes*), and (iii) bony fish (*Osteichthyes*).

Fish that are predominantly farmed and eaten are bony fish. Consequently, it was proposed that MRLs extrapolation in fish should be limited to this class.

The general and specific criteria included in the approach adopted by Codex are summarized below:

General criteria

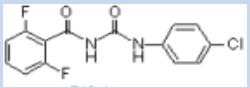
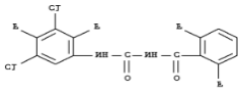
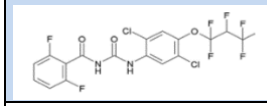
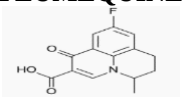
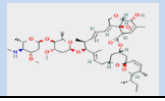
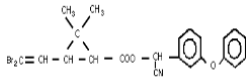
1.	Extrapolation takes place only between the same tissues/food commodities in the reference and concerning species
2.	Extrapolation concerns species on a one-to-one basis
	The reference and concerning species are related: metabolism does not vary significantly within the group of related species. that the M:T established for the reference species can be applied to the concerned species
	The marker residue in the reference species is the parent compound only
	or is the same as the total residues of toxicological concern,
	or the Codex MRL status in the reference species is 'unnecessary' and there is an expectation that the active substance will be used under the same conditions
	The M:T established for the reference species can be applied to the concerned species
Specific criteria	
3.	Identical Codex MRLs have been established in at least two related species on the basis of JECFA recommendations or there is good reason to consider extrapolation from just one related species

	The most conservative set of Codex MRLs can be extrapolated to other related species when identical M:T values have been used in JECFA calculations for two related species but the MRLs recommended (by JECFA) differ.
	The same Codex MRLs can be extrapolated to related species when the M:T established by JECFA is 1 in all tissues in a single reference species.
Additional criteria	
4.	For bony fish: where the MRL in muscle/fillet recommended by JECFA was established based on the limit of quantification (LoQ) (e.g., twice the LoQ), the MRL can be extrapolated to all bony fish

6. Application of the MRLs extrapolation methodology for selected candidate Vet drugs

Considering the Vet drugs of interest to the aquaculture sector in the Arab region with the existence of MRLs established by CODEX, we applied the extrapolation approach on these drugs using the criteria established by Codex summarized in table 8 below.

Table 8: Application of MRL extrapolation for the candidate compounds in compliance with CCRVDF principles

CANDIDATE	MRLs already established in muscle/fillet of bony fish species?		Species concerned	Is the marker residue the parent compound?	M:T exist in muscle/fillet of 2 bony fish species	M:T =1 in the reference species. And MRLs have been established for one species	The MRL in the reference species was established based on the twice the LoQ	Recommendation related to the application of the extrapolation approach and proposed MRL
	full evaluation undertaken by JECFA?	Which reference species have MRLs been established in?						
DIFLUBENZURON 	Yes JECFA 81 (2015) JECFA 88 (2019)	Salmon (muscle and skin in natural proportions)	All Finfish	Yes	No	M:T is close to 1 (0.9) established by JECFA for salmon during its 88th meeting.	-	Yes 10 µg/kg for fillet and muscle
TEFLUBENZURON 	Yes JECFA 81 (2015)	Salmon (muscle and fillet)	All finfish	Yes		M:T is close to 1 (0.8 calculated in muscle and skin in natural proportion of salmon).		Yes 400 µg/kg for fillet and muscle
LUFENURON 	Yes JECFA 85 (2017)	Salmon and trout	All finfish	Yes	Yes	An M:T value of 1.0 was calculated for salmon		Yes 1350 µg/kg for muscle and skin in natural proportion
FLUMEQUINE 	Yes JECFA 42 (1994); 48 (1997); 54 (2000); 60 (2002); 62 (2004); 66 (2006) EU, Japan	Cattle; chicken; pig; sheep Trout (muscle)	All Finfish	Yes		The M:T in trout is most probably 1 (suggesting no significant metabolism in fish) and, in addition, identical MRLs have been established in multiple unrelated species.		Yes 500 µg/kg for muscle
EMAMECTIN BENZOATE 	Yes JECFA 78 (2013)	Salmon and trout (muscle and fillet)	All finfish	(Emamectin B1a)		The M:T is close to 1 (0.9) in muscle and fillet of salmon		Yes 100 µg/kg for fillet and muscle
DELTAMETHRIN 	Yes JECFA 52 (1999); 60 (2003)	Cattle; chicken; sheep Salmon (muscle)	All finfish	Yes			The concentrations of the marker residue and total residues were very low in muscle (of all species), with the MRL established based on	Yes 30 µg/kg for muscle

CANDIDATE	MRLs already established in muscle/fillet of bony fish species?		Species concerned	Is the marker residue the parent compound?	M:T exist in muscle/fillet of 2 bony fish species	M:T =1 in the reference species. And MRLs have been established for one species	The MRL in the reference species was established based on the twice the LoQ	Recommendation related to the application of the extrapolation approach and proposed MRL
	full evaluation undertaken by JECFA?	Which reference species have MRLs been established in?						
							twice the LoQ	

Conclusion:

To apply the Codex MRLs extrapolation approach, we considered the different criteria defined in the codex principles related to finfish and also the main vet drugs used in aquaculture of High concern for the countries specially for the MENA region. For this purpose, we used scientific research, available data and reports established by international agencies (FAO, Word bank, JECFA, WHO report, etc.).

According to our findings, the MRL extrapolation approach established by Codex can be applied to finfish for some vet drugs of interest in the aquaculture industry in the MENA region. It concerns the following compounds: ***Deltamethrin, Flumequine, Lufenuron, Teflubenzuron, Emamectin Benzoate and Diflubenzuron***.

The proposed MRLs resulting from this approach for the species cultured in the region are presented below and may be considered for adoption as ***provisional MRLs in the Arab region****, until further data may be available specifically for these substances and the relevant species.*

SUBSTANCE	*Aquaculture Finfish of interest in the Arab region*	*Proposed MRL*
DIFLUBENZURON	*Tilapia, Seabass, Trout, Seabream*	10 µg/kg for fillet and muscle
TEFLUBENZURON	*Tilapia, Seabass, Trout, Seabream*	400 µg/kg for fillet and muscle.
LUFENURON	*Tilapia, Seabass, Seabream*	1350 µg/kg for muscle plus skin in natural proportion
FLUMEQUINE	*Tilapia, Seabass, Seabream*	500 µg/kg for muscle
EMAMECTIN BENZOATE	*Tilapia, Seabass, Trout, Seabream*	100 µg/kg for fillet and muscle
DELTAMETHRIN	*Tilapia, Seabass, Trout, Seabream*	30 µg/kg for muscle

However, this approach would not provide guidance on the good veterinary practices to apply, in particular, the withdrawal period to be followed, such that these MRL values are achieved. Regulatory jurisdictions are advised to access the relevant data and applicable practices to set these requirements.

The proposed MRL extrapolation approach offers a suitable solution to develop standards needed at the regional level, addressing the needs of the aquaculture industry in the MENA region. Such standards derived on the basis of an agreed-up methodology underpinned by a Codex guidance would be considered scientifically robust and therefore more likely to be accepted by various countries in the region and around the world, hence contributing to the trade of these commodities at the intra-regional and international level.

Appendix 1: Summary of steps leading to the development of the MRL extrapolation approach under CCRVDF

Table 9: The main aspects discussed and the decisions made by CCRVDF concerning MRL extrapolation

Committee	Discussion and decisions of the committee
CCRVDF 19, 30 August – 3 September 2010 **(**REP11/RVDF)	The question regarding the possibility to establish MRLs by extrapolating was raised during the discussion of the need to establish MRLs for *Triclabendazole* in goat tissues. The JECFA Secretariat informed the Committee that EHC 240 included principles for extrapolation of MRLs for veterinary drugs residues and pesticides. The Committee agreed to consider the development of a policy for extrapolation of MRLs to additional species and tissues and to consider the European Union's experience in the establishment of a policy for extrapolation of MRLs. ***Committee decision*** *To establish an **EWG**, led by Canada, with the following tasks:* ➢ *Collate and summarise all the available national and regional guidelines and documents and published literature pertinent to the extrapolation of MRLs;* ➢ *Prepare a list of substances with existing MRLs in a number of species/food matrices for which extrapolation is considered necessary and make a proposal for prioritization;* ➢ *Prepare recommendations for the CCRVDF to request JECFA to consider whether EHC 240 provides sufficient guidance for JECFA to develop a scientific framework for extrapolating MRLs between species and tissues, or whether additional scientific considerations are required;* ➢ *Propose a potential risk analysis policy for use by CCRVDF when considering extrapolating MRLs.*
CCRVDF 20, 7-11 May 2012 (REP12/RVDF)	*The EWG presented the outcome of their work, notably the proposed policy for extrapolation (CRD30), the list of veterinary drugs proposed as a priority for MRL extrapolation (CX/RVDF12/20/15, Appendices 1a and 2b), and the criteria for the prioritization of compounds for inter-species MRLs extrapolation.* ***Committee decision*** *The Committee agreed not to consider the list of substances and to forward questions related to the adoption of MRLs extrapolation and the proposed Risk Analysis Policy on Extrapolation of MRLs of Veterinary Drugs to Additional Species and Tissues to JECFA for advice.* *A **physical Working Group**chaired by Canada was established to revise the policy in light of the comments submitted and the advice by JECFA, if available.*
CCRVDF 21, 26 – 30 August 2013 (REP14/RVDF)	The Committee considered the recommendations of the EWG[1] notably the amended draft Risk Analysis Policy proposed in light of the comments received from JECFA on the questions put forward at the last session.

[1] CX/RVDF 12/20/15

	The Committee agreed not to have a separate Risk Analysis Policy but to include provisions on extrapolation within the Principles of Risk Analysis applied by the CCRVDF. The Committee discussed whether the terms extrapolation and extension could both be used. *The Committee agreed to forward questions to JECFA to request the completeness and amendment of the extrapolation principles described in EHC 240 about the following considerations:* *a) Clarification of the reference "metabolic profile between species";* *b) Establishment of the criteria/assumptions to be used for interspecies extrapolations, including minimum data required to support such extrapolation among physiological related species, and extrapolation to additional (unrelated) species;* c) *Possibility of extending extrapolation similar to that allowed under the current EU guidelines: to allow the extrapolation of MRLs from the muscle of Salmonidae to other fin fish; to consider the extrapolation of MRLs between fish species. Further work was required if the data to support such MRL extrapolation was not deemed available, and a question remained as to whether MRLs can be extrapolated to all food-producing species when the established MRLs in three different "classes" of major species (ruminant, pigs, and chickens) are similar.*
CCRVDF 22, 27 April – 1 May 2015 (REP15/RVDF)	The 78th JECFA addressed the comments and questions of CCRVDF21 and prepared guidance on the criteria and principles applied by JECFA for extrapolation. JECFA mentioned that the term extension will be used when sufficient depletion data are available for the minor species to permit the derivation of MRLs while the term extrapolation will be used when the depletion data are insufficient. *During the discussion about the Priority List of Veterinary Drugs Requiring Evaluation or re-evaluation by JECFA, the committee addressed a request to JECFA on MRLs for Generic Fish Species:* ➢ *To amend the request for MRLs for amoxicillin for "flat fish" as opposed to "finfish" and to explore the possibility to extrapolate the MRLs to other finfish;* ➢ *To provide an assessment on whether, on the basis of data from one or more fish species, it is possible to establish an MRL for finfish, crustaceans, or molluscs in general, or for multiple similar groups.* ➢ *For Emamectin benzoate, to provide an assessment as to whether there are any identified toxicological, dietary exposure modeling, or analytical methodology issues preventing extrapolation of the proposed MRLs to a general finfish MRLs or a more appropriate sub-grouping.*
CCRVDF23, 17 – 21 October 2016 (REP17/RVDF)	In order to properly address the issue of extrapolation of MRLs to fish species, the 81st JECFA required further information on adequate groupings of fish species so that representative species could be identified from which MRLs could then be extrapolated to other similar species. *To respond to the request of the 81st JECFA, the Committee agreed to establish an **EWG**, chaired by Norway and co- chaired by Japan, to: Develop a discussion paper on the feasibility of establishing MRLs for groups of fish species for veterinary drugs being considered by JECFA/CCRVDF and to consider what grouping might be appropriate for finfish, crustaceans and mollusks.*

CCRVDF24, 23 – 27 April 2018 (REP18/RVDF)	At CCRVDF24, the discussion paper prepared by the EWG on MRLs for groups of fish species was discussed, notably the options and views on the need for grouping as well as the challenges and limitations including the need to consider the appropriateness of basing the extrapolation on the classification of the fish on the draft VICH GL57. Otherwise, the EWG mentioned that among the **50 registered medicines for fish or crustaceans requested for MRLs**, only **5 compounds were given MRLs by Codex** "*The major target fish orders submitted were Perciformes (30 compounds), Salmoniformes (28 compounds), and Decapoda (19 compounds). This shows a need for extrapolation for compounds not yet evaluated by JECFA".* The committee observed that the desirability of extrapolating MRLs was not limited to fish species, but also other animals, noting the extensive list of compounds on countries' needs for MRLs. **As a result, a policy for extrapolation of MRLs for all species was suggested. It was also recommended that a pilot on extrapolation of some compounds for which there were already MRLs for a particular fish species to other fish species or orders of fish (e.g. deltamethrin, flumequine, and teflubenzuron) be undertaken.** In order to provide more autonomy to the committee, CCRVDF decided to amend the section of Risk Analysis Principles (Procedural Manual, Section IV) which requires that extrapolation of MRLs to one or more species could only be recommended where JECFA had identified that it is scientifically justifiable and the uncertainties have been clearly defined. ***The main decisions of CCRVDF held during CCRVDF24:*** *a) to forward an amendment to section 3.4, paragraph 30 of the Risk Analysis Principles applied by CCRVDF for adoption by CAC41 (Appendix V of the CCRVDF24 report);* *b) to establish an **EWG**, chaired by the EU, with the following TORs:* **Prepare a discussion paper to explore pragmatic ways on how CCRVDF in its role as risk manager could extrapolate MRLs to one or more species;* **Prepare and contrast such approaches with the revised option c for aquatic species;* **Conduct a pilot on extrapolation of MRLs identified in the priority list Part D (Appendix VI of the CCRVDF24 report).*
CCRVDF25 held virtually 12 – 16 and 20 July 2021 **(**REP21/RVDF)	The EWG presented the outcome of their work and the revised approach of MRLs extrapolation (CRD3). The EWG informed CCRVDF that in relation to the extrapolated MRLs, all 10 from the ruminant group could be extrapolated, but only 2 out of the 3 for the fish group. Concerning the Extrapolated MRLs, due to time constraints CCRVDF was unable to consider the proposals for the extrapolated MRLs and agreed that the MRLs would be circulated for comments and further consideration by the EWG. There was wide support in both the EWG and the informal online discussion group for the proposed approach, but that there were some outstanding issues discussed, and an amendment was adopted to the initial proposal. The approach proposed by EWG was revised to include in addition the following:

	➢ to clarify that when 2 reference species are used, it is acceptable for the MRL for one reference species to have been derived by extension from the other; ➢ refer to use the term finfish rather than bony fish and to delete reference to the scientific names as existing Codex MRLs for veterinary drugs mainly apply to finfish; ➢ adopt a more flexible approach by indicating that extrapolation could also be from just one related species under certain circumstances; ➢ delete the reference to "or approaching 1" as this related to expert judgement, so by deleting this sentence, experts could still accommodate some flexibility in complying with the JECFA practice that the M:T should be equal to 1 when extrapolating MRLs between similar species; and ➢ note to explain that it was important to harmonize terms for edible tissue as this was important especially in the case of fish and the use of terms muscle and fillet. *The main decisions of CCRVDF:* *a) forward the approach for extrapolation as revised to CAC44 (2021) for adoption and inclusion as Annex C to the Risk Analysis Principle Applied by CCRVDF (Appendix III);* *b) to include a footnote in paragraph 30, 2nd bullet point of the principles the following: the approach for the extrapolation of MRLs for veterinary drugs to one or more species is presented in Annex C to these principles" as a consequential amendment for adoption by CAC44 (Appendix III);* *c) request the Codex Secretariat to issue the proposed extrapolated MRLs for comment through a CL; and REP21/RVDF 13* *d) re-establish the **EWG**, chaired by the European Union, and co-chaired by Costa Rica, to continue discussing the extrapolated MRLs considering the comments submitted to the aforementioned CL, and prepare revised proposals for consideration by CCRVDF26.* At its 44th session, the CAC44 adopted the Amendment to the Procedural Manual, Risk Analysis principles applied by CCRVDF: Approach for the extrapolation of MRLs for veterinary drugs to one or more species, as presented by CCRVDF (REP21/RVDF, paragraph 105(i,ii), Appendix III).
CCRVDF26 – Planned physical meeting from 13/02/2023 to 17/02/2023	As agreed by CCRVDF25, a circular letter was prepared and addressed by the Codex Secretariat to issue the proposed extrapolated MRLs for comments. Delegates and observers were invited to provide comments on the proposals for MRLs extrapolation for the different combinations of veterinary drugs/tissues represented by 12 vet drugs among which 2 compounds are for finfish (Flumequine and deltamethrin). The EWG chaired by the European Union, and co-chaired by Costa Rica, will present the extrapolated MRLs considering the comments submitted in response to the CL, and will present to the committee the revised proposals for consideration by CCRVDF26.

Appendix 2: Application of the CRVDF guidance on extrapolation of maximum residue limits of veterinary drugs to one or more species

Considering the criteria defined on the basis of the approach of MRLs extrapolation, the EWG established by CCRVDF24 used the extrapolation methodology as a pilot to address the MRLs identified in Part D of the Priority List established by CCRVDF24. Two MRLs for bony fish (Deltamethrin and Flumequine) were considered for extrapolation, the proposed MRLs are planned for discussion at the upcoming session of CCRVDF (CCRVDF26).

The proposed MRLs are presented in the table below:

Table 10: Candidate MRLs developed according the methodology of extrapolation by the EWG (CX/RVDF 21/25/8).

Compound / Proposed MRL extrapolation	Species that MRLs are established in	The main considerations	Proposed MRLs
Deltamethrin Muscle: 30 (µg/kg)	Salmon Muscle: 30 (µg/kg)	➢ Full evaluation undertaken by JECFA ➢ The marker residue is the parent compound ➢ The concentrations of the marker residue and total residues were very low in muscle (of all species), with the MRL established based on twice the LoQ.	The proposed MRL in Muscle for bony fish is 30µg/kg.
Flumequine Muscle: 500 (µg/kg)	Trout Muscle: 500 (µg/kg)	➢ Full evaluation undertaken by JECFA ➢ The marker residue is the parent compound ➢ The M:T in trout is most probably 1 (suggesting no significant metabolism in fish) and, in addition, identical MRLs have been established in multiple unrelated species.	The proposed MRL in Muscle for bony fish is 500 (µg/kg).

Appendix 3: offers examples of Veterinary Drug applications authorized for use in North-African Countries of the Arab region.

Examples of use of vet drugs in some Arab countries

In Tunisia: Only one antibiotic currently has a Marketing Authorization for fish in Tunisia, it is flumequine with the specialty FLUMEXYL®. For the other molecules (oxytetracyclines, potentiated sulfonamides, and oxolinic acid), the use of the cascade principle is systematic, with the use of antibiotics indicated in other species, especially poultry.

In Morocco, the Ministries in charge of Agriculture and Public health are involved in the registration of vet drugs in accordance with legislation, procedures and the texts in force. For this purpose, laboratories are requested to provide a dossier that is submitted to the scientific expertise of the various specialists of the two Departments, which contain all the relevant information, notably pharmaco-toxicological studies and preclinical and clinical trials for the originator product. At the end of the evaluation, each of the two Departments presents its report to the Commission Joint Marketing Authorization for Veterinary Medicinal Products. The Commission then issues an opinion: granting of the marketing authorisation, adjournment or refusal. Actually, only three compounds have been registered: **ATLASCORBIC** (Ascorbic acid), **FLUQUICK 50 POUDER** (Flumequine) and **TS 48 (**Sulfadiazine sodium -Trimethoprim).

Appendix 4: CCRVDF's Database on countries 'needs

To allow prioritization of veterinary drugs for evaluation by JECFA, CCRVDF conducted a survey action to update the Database on countries' needs for MRLs based on the comments submitted by delegates to CCRVDF, identified as a high-priority needed MRLs (CX/RVDF 16/23/9 Add.1). The major compounds are antimicrobial agents represented by among 13 active substances needed for breeding fish species (like finfish, salmonids, catfish, etc.)), presented in the table 11 below:

Table 11: List of vet drugs for finfish required for MRLs extracted from CCRVDF Database on countries' needs survey established during the 23rd session
(CX/RVDF 16/23/9 Add.1)

No	Name	Species	Countries Requesting	JECFA Evaluation / Codex MRLs	Country MRLs
1	**Florfenicol**	Fish Muscle	Peru, Republic of Korea and Belize	**No Codex MRLs**	Australia; Canada: salmonids; EU: finfish; USA: catfish, salmonids; Republic of Korea (0.2-fish)
2	**Erythromycin**	Fish Muscle	Indonesia Fish species: Nile tilapia, milkfish, walking catfish, gouramy, common carp, barramundi, grouper	66th JECFA, 2006; Full ADI **No Codex MRLs**	Indonesia
3	**Enrofloxacin**	Fish Muscle	Indonesia Fish species: Nile tilapia, milkfish, walking catfish, gouramy, common carp, barramundi, grouper	48th JECFA, 1997; Full ADI **No Codex MRLs**	Indonesia
4	**Chlorteracycline**	Fish Muscle	Indonesia Fish species: Nile tilapia, milkfish, walking catfish, gouramy, common carp, barramundi, grouper	51st JECFA, 1998; Full ADI **No Codex MRLs**	
5	**Tetracycline**	Fish Muscle	Indonesia Fish species: Nile tilapia, milkfish, walking catfish, gouramy, common carp, barramundi, grouper	Tetracyline: 50th JECFA 1998; Full ADI. Oxytetracycline: 50th JECFA, 1998; 58th JECFA, 2002; Full ADI. **No Codex MRLs (only for oxytetracycline)**	Indonesia

6	**Sulfamdimethoxine**	Fish (all species)	Democratic People's Republic of Korea	**No Codex MRLs**	Canada: cattle, swine, horse, chicken, turkey; **EU:** all food producing species; USA: chicken, turkey, cattle, duck, salmonids, catfish, chukar partridges
7	**Oxolinic Acid**	Finfish, Salmonids Muscle and Skin	Chile, Republic of Korea	43rd JECFA, 1994; No ADI **No Codex MRLs**	EU; Republic of Korea (0.1- cherry salmon, salmon, yellowtail, eel, ayu sweetfish, carp); Japan
8	**Flumequine**	Salmonids Muscle and Skin, in natural proportion	Chile	66th JECFA, 2006; Full ADI Codex **MRLs in cattle, pig, sheep, chicken, and trout**	EU, Japan
9	**Trimethoprim**	Every producing food species Muscle and Skin, in natural proportion	Morocco	**No Codex MRLs**	Australia: mammals, poultry; Canada: salmonids; EU: horse, all other food producing species
10	**Sulfamethoxypridazine**	Every producing food species	Democratic People's Republic of Korea	**No Codex MRLs**	EU: all food producing species; USA: swine, cattle
11	**Sulfamerazine**	Every producing food species	Democratic People's Republic of Korea	**No Codex MRLs**	Canada: cattle, sheep, pig; EU: all food producing species
12	**Phosphomycin**	Aquaculture Muscle and Skin	Argentina	**No Codex MRLs**	Japan
13	**Norfloxacin**	Aquaculture Muscle	Belize	**No Codex MRLs**	
14	**Colistin**	All livestock	Armenia	66th JECFA, 2006; Full ADI **Codex MRLs in cattle, pig, sheep, goat, rabbit, chicken, and turkey**	Armenia; EU: all food producing species

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