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Overview of International Regulations for Biologicals

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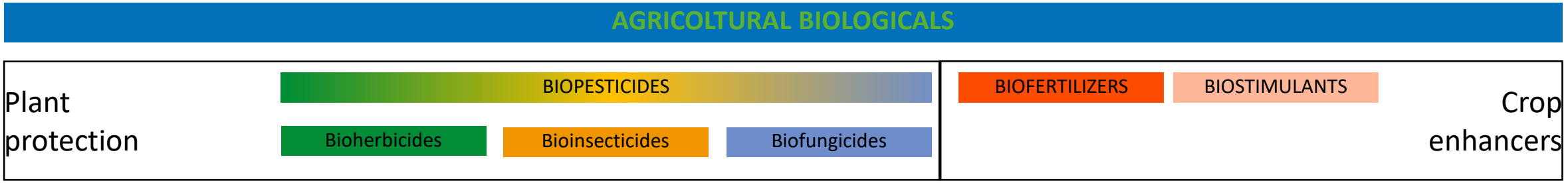
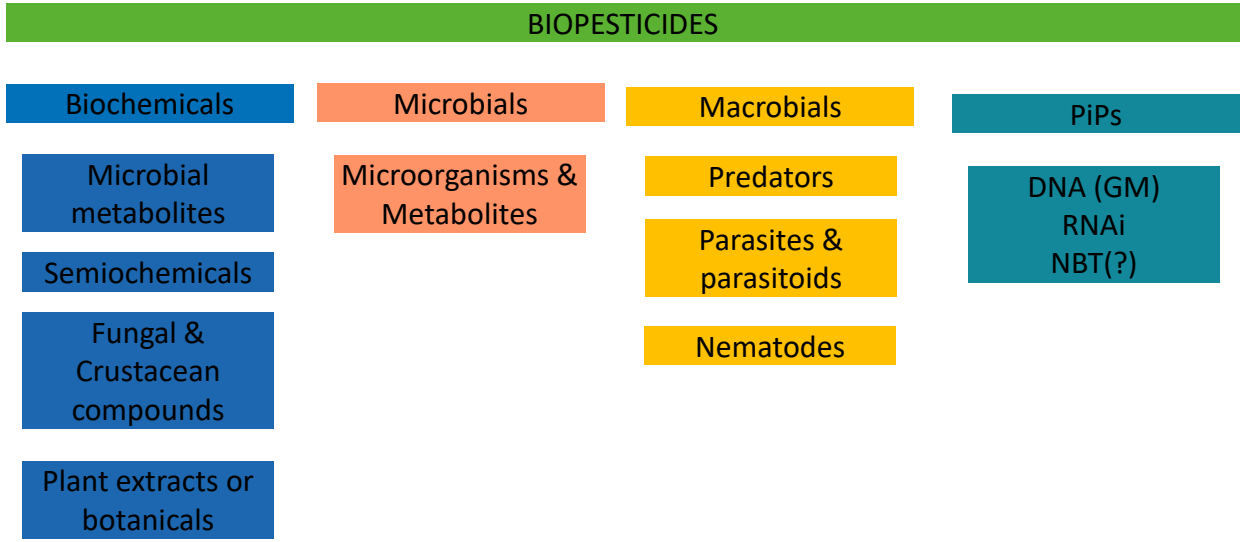
Presentation Outline

1. High overview of agricultural biologicals
2. Principles for registration of biological products
3. Global registration requirements (WHO/FAO, EU, US)
4. Global channel-of-trade requirements
5. Conclusion & Recommendation

What are the agricultural biologicals?

Agricultural biologicals are biological agents, substances, or mixtures used to prevent, destroy, or control pests, weeds and diseases, or biological substances or microorganisms capable of promoting crop health (crop enhancers) by increasing the availability of nutrients (biofertilizers) or by acting as plant strengtheners and phytostimulants (biostimulants)





Biochemicals are naturally occurring substances that control pests by non-toxic mechanisms such as pheromones, biocontrol compounds isolated from microorganisms or fungi or crustacean shells (chitosan), plant extracts including alkaloids, terpenoids and phenolics and natural occurring minerals.

Microbials are microorganism and their metabolites produced by these organisms exendin biopesticidal action

Macrobials are natural predators that can reduce crop pests: predators, parasites and nematodes

Plant-incorporated Protectants (PIPs) are substances produced by plants from added genetic material providing a built-in pest control. Genes from bacillus thuringiensis are frequently used to create PIPs.

BIOPESTICIDE TIMELINE ADOPTION

biologicals

100 MY — Plants developed inducible defense responses

10 KY — Crop domestication

4,50 KY — Sulphur used by Sumer to dust crops

4-2 KY — Neem tree extracts and other botanicals used in Egypt, China, Greece and India

400 BC — Weaver ants used in China and Southeast Asia a biocontrol agent in citrus

C15th — Documented use of arsenic, lead and mercury

C17th — Nicotine sulfate used to control plum beetles

C19th — Pyrethrum and rotenone used

1835 — **A. Bassi** using *Beauveria bassiana* shown to cause disease of silkworms

1874 — **Pasteur** and **Le Conte** suggested using fungi to control insects

1879 — **Ilja I. Metschnikow** attempted to use ***Metarhizium anisopliae*** against the wheat chafer

1901 — **Shigitane Ishitawa** isolated *Bacillus thuringiensis* from a silkworm

1904 — Rodenticide based on *Salmonella enterica* used in Sweden and other EU Countries

1911 — First attempts to use bacteria against insects in Mexico and South America

1930 — *Steinernema* nematodes isolated by **Glaser** and **Fox**

1930s — *Trichoderma* used as biofungicide

1938 — First Bt product "Sporeine" sold in France

1948 — *Bacillus popilliae, B. lentinomorbus and B. thuringiensis* registered in USA for insect control

1971 — *B. subtilis* identified as biofungicide

1973 — *Heliothis* NPV first viral insecticide "Elcar"

1977 — *Bacillus thuringiensis* var. *israelensis* (toxic to flies) discovered

1979 — EPA registered 1st insect pheromone as a biopesticide

1980 — First protozoan *Nosema locustae* registered for grasshopper control

1990s — Biopesticides in IPM

1996 — Bt GM crops

2000 — Biopesticide Industry Alliance Standards established

2009 — EU adopts Sustainable Use Directive

Advantages and disadvantages of biopesticides

Biopesticides are associated with perceived attributes (positive and negative) which currently influence market attitudes

Perceived advantages are:
Low environmental risk
Low mammalian risk
Non target safety
Lower resistance development
Less residues
Usable against a pest where parasitoids or predators are also active

Perceived disadvantages are:
Low efficacy compared to chemicals
Variability in performance
Slow to kill
Limited shelf life
Often targets niche markets
Low persistence after application

But within IPM strategies they offer:

Flexible treatment options: perfect to manage PHI
Diverse pest management: to control chemical resistant pest populations and protect against future developments through rotation
Fewer applications and smaller quantities of pesticides applied: to decrease labor and time spent applying conventional pesticides
Sustainable and environmentally responsible: meet consumer demands for the environment and future demand of natural resources
Enhance a variety of crops: using a product applicable on a variety of different crops

2. Core principles for registration of a biological product

Registration of biologicals are based on:

1. Specific benefit claims (value proposition)
2. Mode of action
3. Regulatory requirements in the territory where will be used

Product claims*

Biopesticide	Biostimulant, biofertilizer, soil/ plant amendment, plant inoculant, etc.
1) Kills, mitigates, repels, controls a pest or disease, 2) Through physiological action, accelerates or retards the rate of growth or maturation, or alters the behavior of plants/ produce, i.e. plant growth regulator (PGR), or acts as a 3) defoliant or desiccant	1) No pesticidal, PGR, defoliant or desiccant claim or intent. 2) Support, optimize, improve, natural plant processes to improve one or more of the following plant or soil characteristics: • nutrient availability, uptake, utilization, use efficiency, • abiotic stress reduction • condition and composition of soil for optimal plant growth 3) Action of above results in improved plant growth, development, quality and/ or yield.

**** Few countries have specific regulations for biostimulants and thus regulate as fertilizers, soil amendments, inoculants or similar produtcs***

Territory Registration and Regulatory Requirements

Biopesticide	Biostimulant, biofertilizer, soil/ plant amendment, plant inoculant, etc.
1) Product/ constituents are currently registered as a pesticide or PGR in the territory. 2) Product claims, intent and constituent(s) require registration as a pesticide or PGR in the territory. 3) Territory regulations specify biostimulants, etc. require registration as pesticides or PGRs.	1) Product/ constituent(s) are not registered as a pesticide or PGR in the territory. 2) Product/ constituent(s) are not intended for use as a pesticide or PGR in the territory. 3) Product claims are not recognized as pesticidal in the territory. 4) Product/ constituent(s) are currently registered/ sold as biostimulant, biofertilizer, microbial fertilizer, soil amendment, plant inoculant, microbial inoculant, etc. in the territory.

3. Global definitions/regulations of Plant Biostimulants

Characteristic	EU 2019/ 1009	Draft ISO	Proposed USDA*	EPA Draft Guidance	Canada CFIA	Ecuador	India FCO	South Africa
Includes substances &/or microorganisms	√	√	√	√	√	√	√	√
Benefits independent of nutrient content	√	√	√	√	√	√	√	
Stimulate/ support natural processes	√	√	√	√		√	√	√
Improves nutrient use efficiency	√	√	√	√		√	√	
Improves nutrient uptake		√	√				√	√
Increases nutrient availability	√	√	√		√		√	√
Improves tolerance to abiotic stress	√	√	√	√	√	√	√	√
Improves tolerance to biotic stress				√		√		
Improves crop quality	√	√	√			√	√	
Improves yield	√	√	√		√	√	√	√
Improves plant growth & development & consequential quality & yield		√	√	√		√		√

*USDA proposed definition in consultation with EPA in “Report to President & Unites States Congress on Plant Biostimulants”.

Guidelines for the registration of microbial, botanical and semiochemical pest control agents for plant protection and public health uses

International Code of Conduct on Pesticide Management

Requirements (pg.59-71) are similar to natural & synthetic chemical pesticides: phys-chemical properties, metabolism in plants & animals, residue studies, toxicity/ecotoxicity studies, risk to human and environment.

- compiles global regulation up to 2017 (EU, US, SE-Asia, OECD, EPPO, etc)
- generally low tox-concerns, extrapolation within species is allowed
- studies can be waived with proper justification of insignificant toxicity, or exposure
- biopesticides can go on fast-track processes
- if validated guidelines are not available, in-house studies and expert judgement is allowed
- labels need to specify biological efficacy, resistance prevention, IPM, storage stability
- Composition is expressed for active principle:

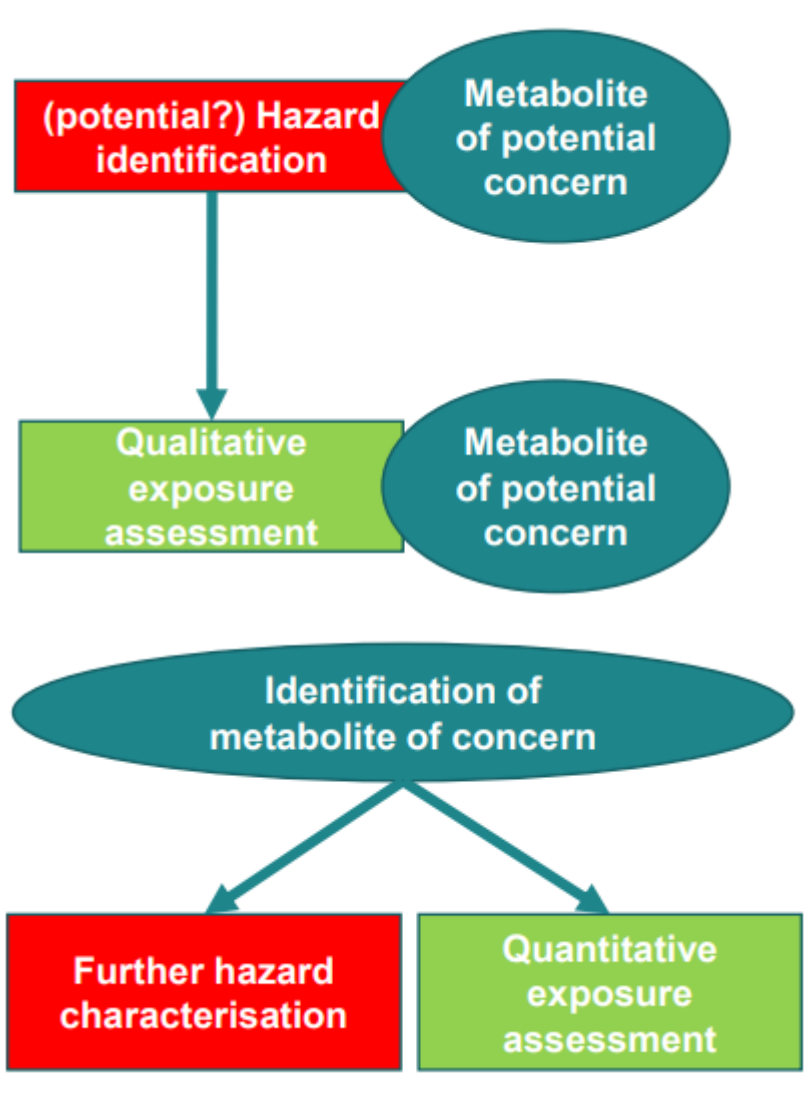
- Microbials: as colony forming unit (CFU) per kilogram/,litre and/or amount of relevant secondary metabolite in terms of biopotency (e.g. Bacillus thuringiensis is expressed in terms of Billions of International Units, or BIU).
- Botanicals: the active substance content can be expressed as the amount of botanical source material, the lead component, or biopotency.
- Semiochemicals: the active substance content is usually expressed as the amounts of each of the active substances or the amount of the combined active substance (e.g. xx g of moth pheromone)

Regulatory Challenges for Biologicals

Coming mainly from EU (e.g. 283/2018 – metabolites of concern)

New scientific approaches are needed:

- Stop mimicking chemical approach
- Evolution of science and technology
- Experience with current applications
- Weight of evidence tox & exposure
- “Need-to-know” approach (i.e. which questions are relevant to answer?)
- Tiered-based approach (mandatory and conditional requirements)
- Increasing quality and stability of products



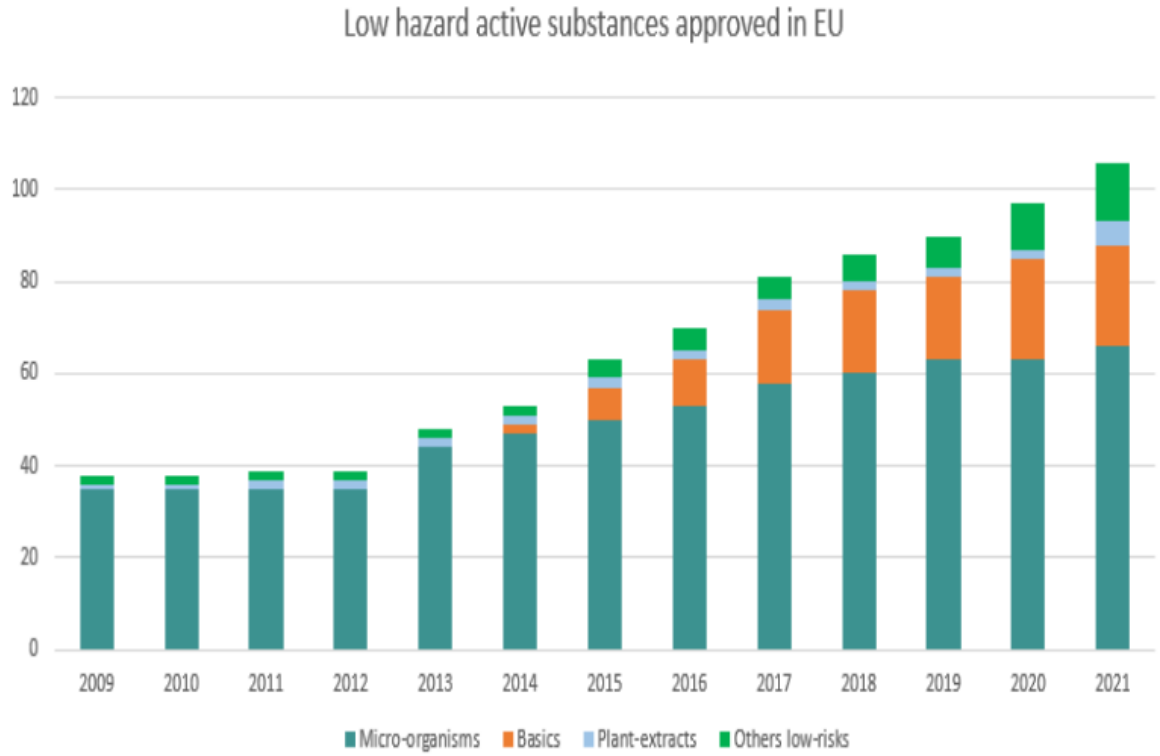
Conditions for Registration of Biologicals in the EU

NON-REGISTRABLE (EU Reg,1107/2009, 546/2011)

- is pathogenic to humans
- is a virus which is infective to humans
- is a bacterium with a known, functional and transferrable gene coding for resistance to relevant antimicrobial agents
- the MO is infective for humans under the recommended conditions of use
- there are not sufficient treatment options against the MO, where relevant based on biological properties
- the MO is pathogenic to non-target organisms (NTO), unacceptable impact on the NTO population

LOW-HAZARD (registrable)

- A micro-organism other than a virus can be low-risk active substance unless its susceptible to 2+ classes of antimicrobials
- A virus may be considered a low-risk active substance if not toxic to NTO and humans.



4. USDA-APHIS requirements for trade of biologicals

The USDA Animal and Plant Health Inspection Service, Plant Protection and Quarantine (USDA-APHIS-PPQ) provides phytosanitary certification of both U.S. and foreign-origin agricultural commodities.

- Plant Protection Act (2000) requires Plant Protection Quarantine (PPQ) 526 permits are required for biologicals not registered by US EPA under:

Registration 40 CFR Part 158:

- Subpart U: Biochemical Pesticides 158.2000
- Subpart V: Microbial Pesticides 158.2100

- Guidance for developing data Biochemical Pesticides Test Guidelines, OPPTS Series 880 and the Microbial Pesticides Test Guidelines, OPPTS Series 885

- IMPORTS : APHIS and U.S. Customs and Border Protection (CBP) accept electronically produced versions of phytosanitary certificates. Acceptable phytosanitary certificates include scanned copies of original certificates, electronic certificates created through ePhyto system, or signed papers.
Certificates should be legible and include APHIS-required statements. Click for details.
- EXPORTS: The export program does not require certification of any U.S. exports, but provides certification of commodities as a service to U.S. exporters.
- Opening New Markets for U.S. Commodities
- Export Program Manual

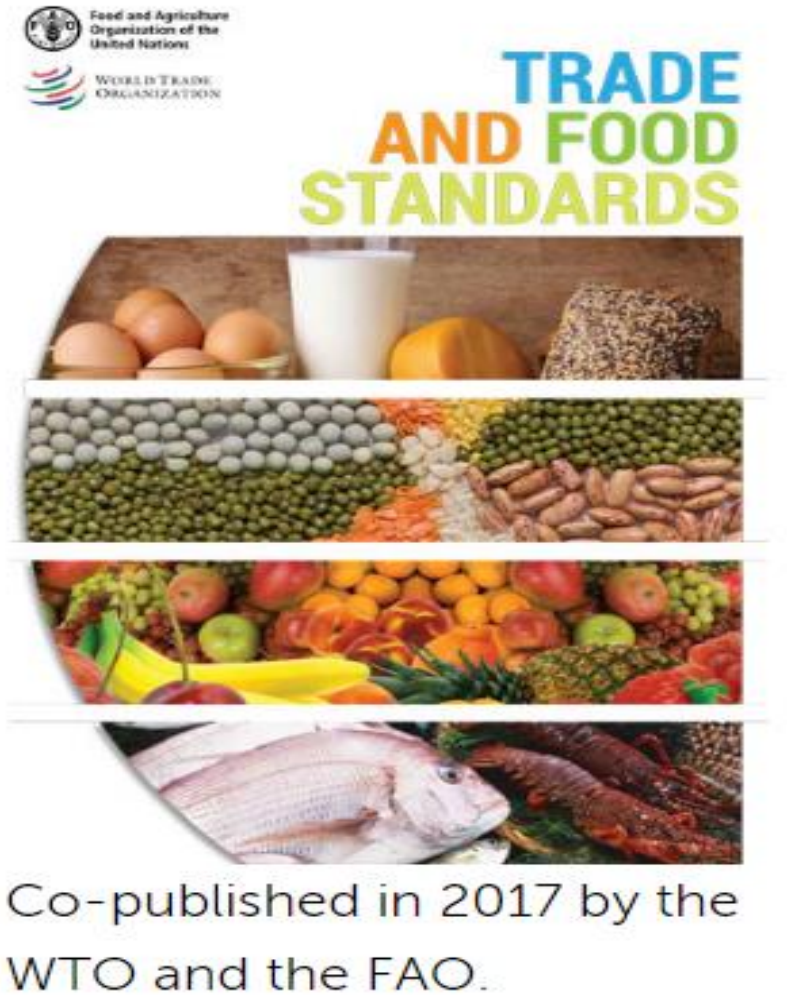
US-FDA requirements for microbiological assays

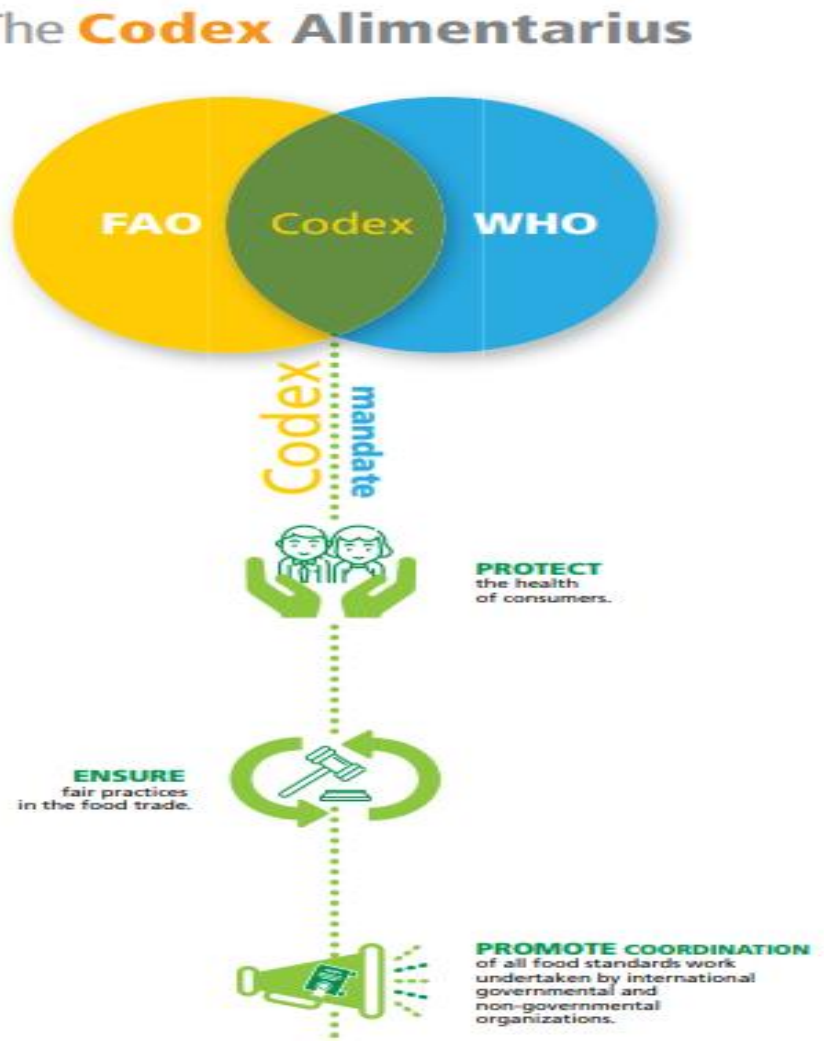
H. Does FDA recommend any specific experimental methods to perform a safety assessment? (link)

We recognize that you can address relevant safety issues for an antimicrobial agent in multiple ways. However, we recommend several resources specific to microbiological methods. FDA publishes an online version of the Bacteriological Analytical Manual which presents useful laboratory procedures (used by FDA labs) for microbiological analyses of foods and cosmetics. Furthermore, FDA maintains a website with links to related resources on Microbiological Methods. Also, (USDA) FSIS maintains a Microbiology Laboratory Guidebook of current protocols for analytical tests FSIS uses in USDA regulated products; these test procedures may be useful in developing protocols to assess technical effect.

- Use a direct method to enumerate microorganisms, such as plate counting or visual microscopic counts, as opposed to measuring biomass; evaluate the reduction (or suppression) of microorganisms affected by the treatment;
- When available, use enumeration methods that capture damaged or stressed microbial cells that survive the antimicrobial treatment;
- For all data, collect and analyze replicate samples and describe the variability of the data;
- Use statistical analyses to compare data from the treated samples to data from controls.

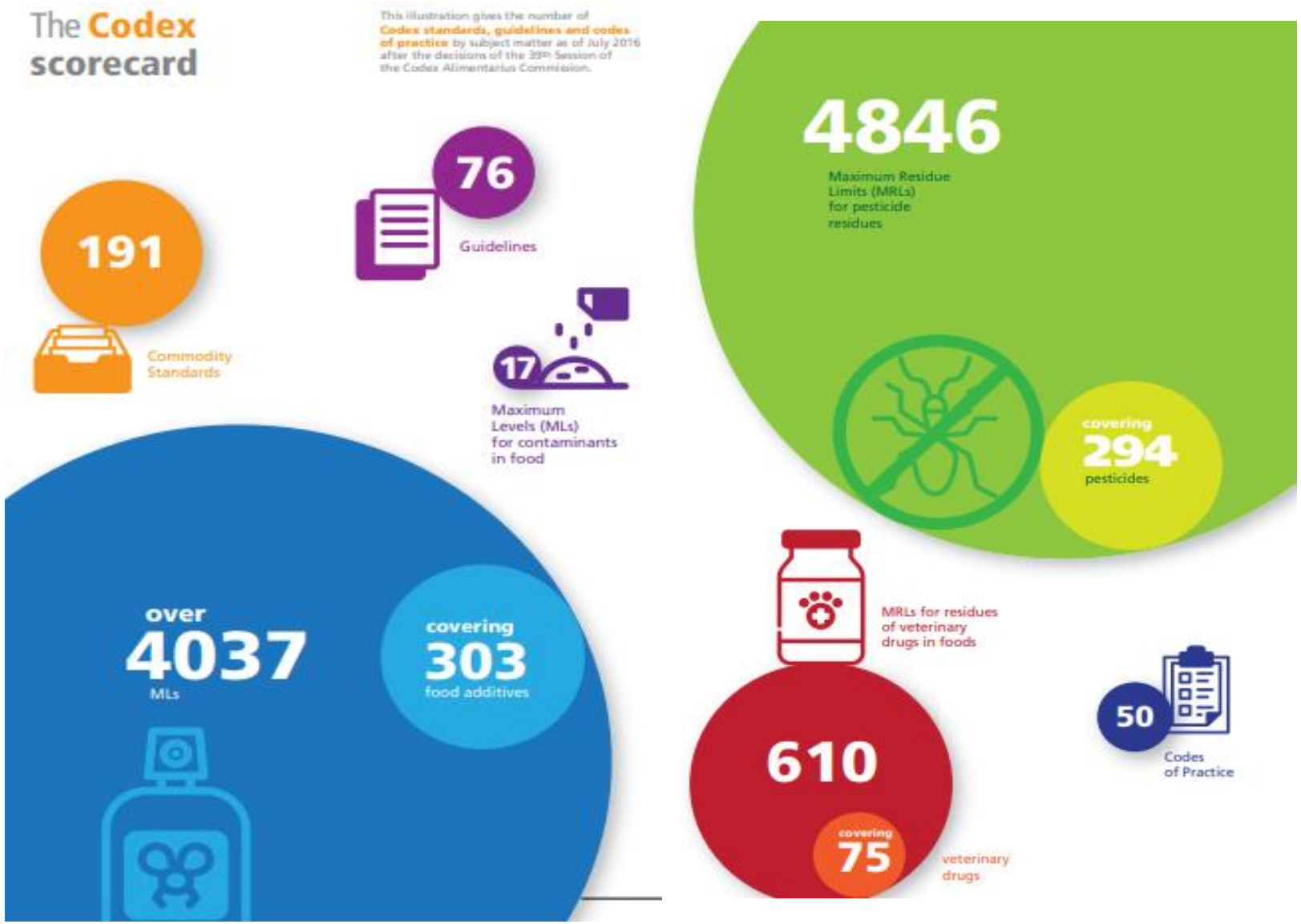
Global Trade and Food Standards (WTO, FAO, WHO) link



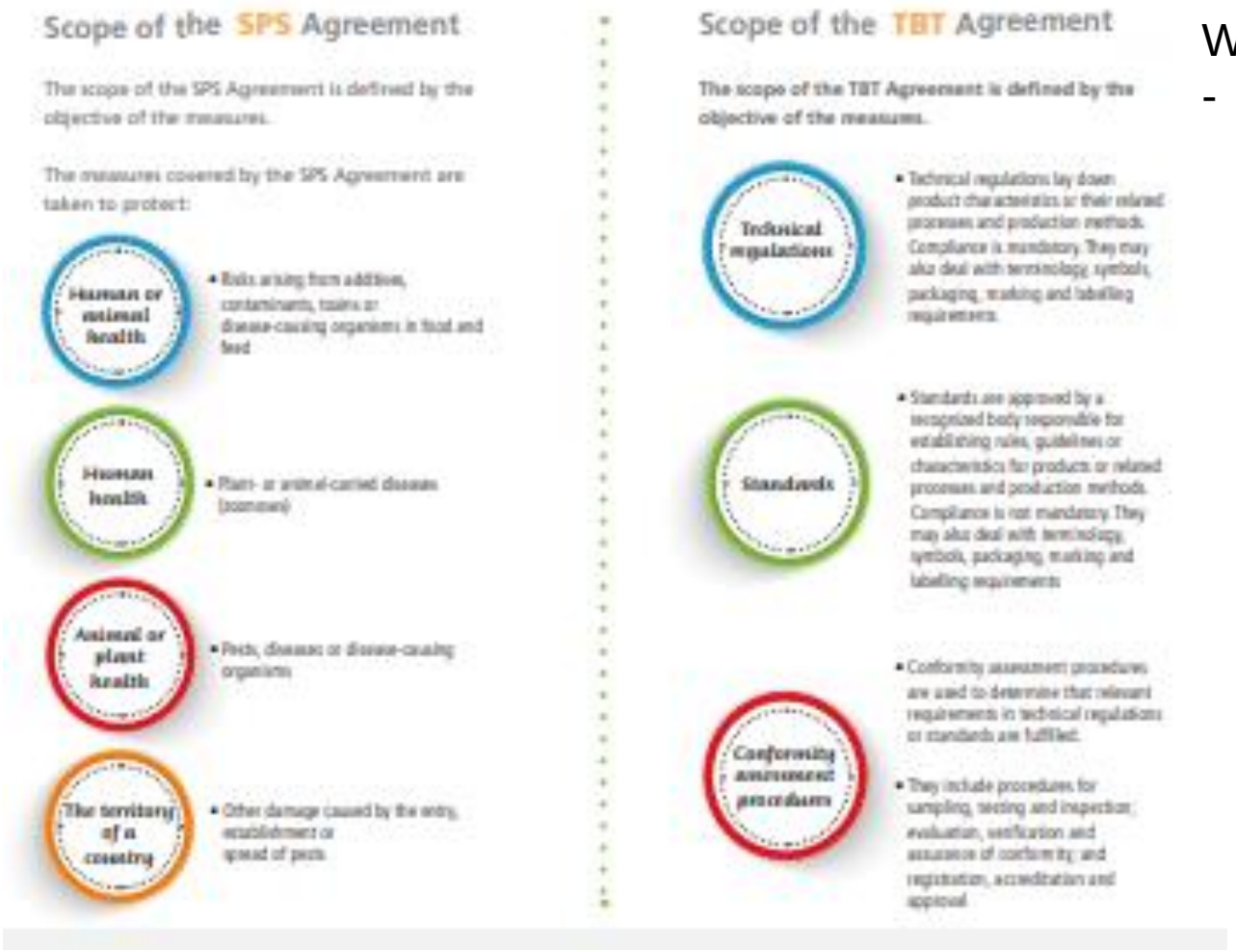


Codex's Scorecard

Microorganisms covered under Contaminants
- CCCF/JECFA
- no MRLs applicable
- AMR concerns



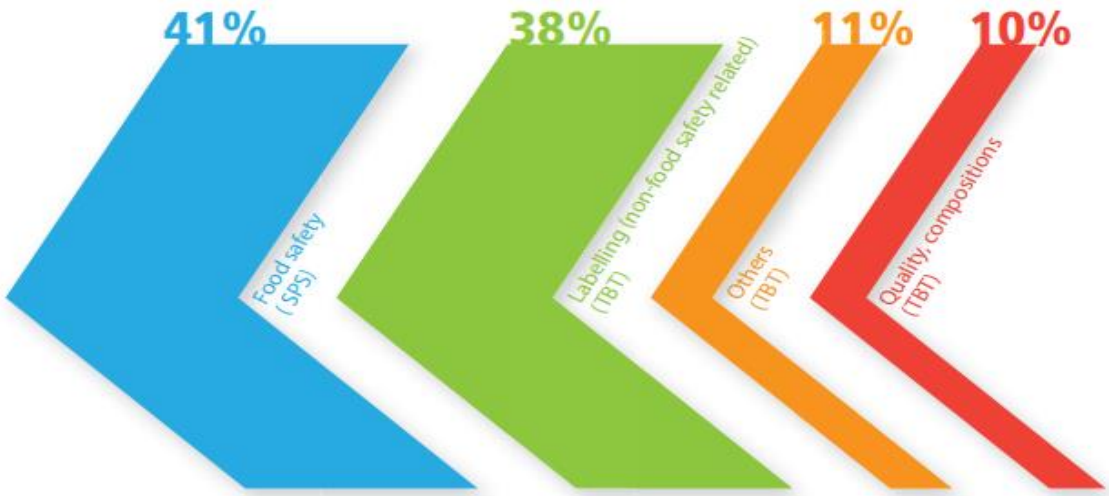
Enforcement of Codex Standards



WTO receives 3,500+ SPS and TBT notifications per year

- Three public online tools compile notifications:
  - the SPS Information Management System (IMS) www.spsims.wto.org
  - the TBT IMS www.tbtims.wto.org
  - ePing SPS/TBT Notification Alert System www.epingalert.org

Figure 4: Specific trade concerns referencing Codex Standards raised from 2012 to 2016 *



WHO Estimates of global burden of food-borne diseases, 2015

The public health burden of food-borne diseases is comparable in magnitude to those caused by tuberculosis, malaria and HIV/AIDS

- One in ten people fall ill every year from eating contaminated food, with 420,000 dying as a result.

- Children aged under 5 are at high risk, accounting for 1/3 of the deaths even though they make up only 9% of the population.

Risk analysis can be used to support strong programmatic and policy decision making in the local context, in the area of standard setting or with regard to which surveillance programs to be prioritized.

Link

World Health Organization

Microbiological Risk Assessment (MRA) in Food, FAO/WHO 2021

Microbiological Risk Assessment in Food Guideline, publication

and **Poster**

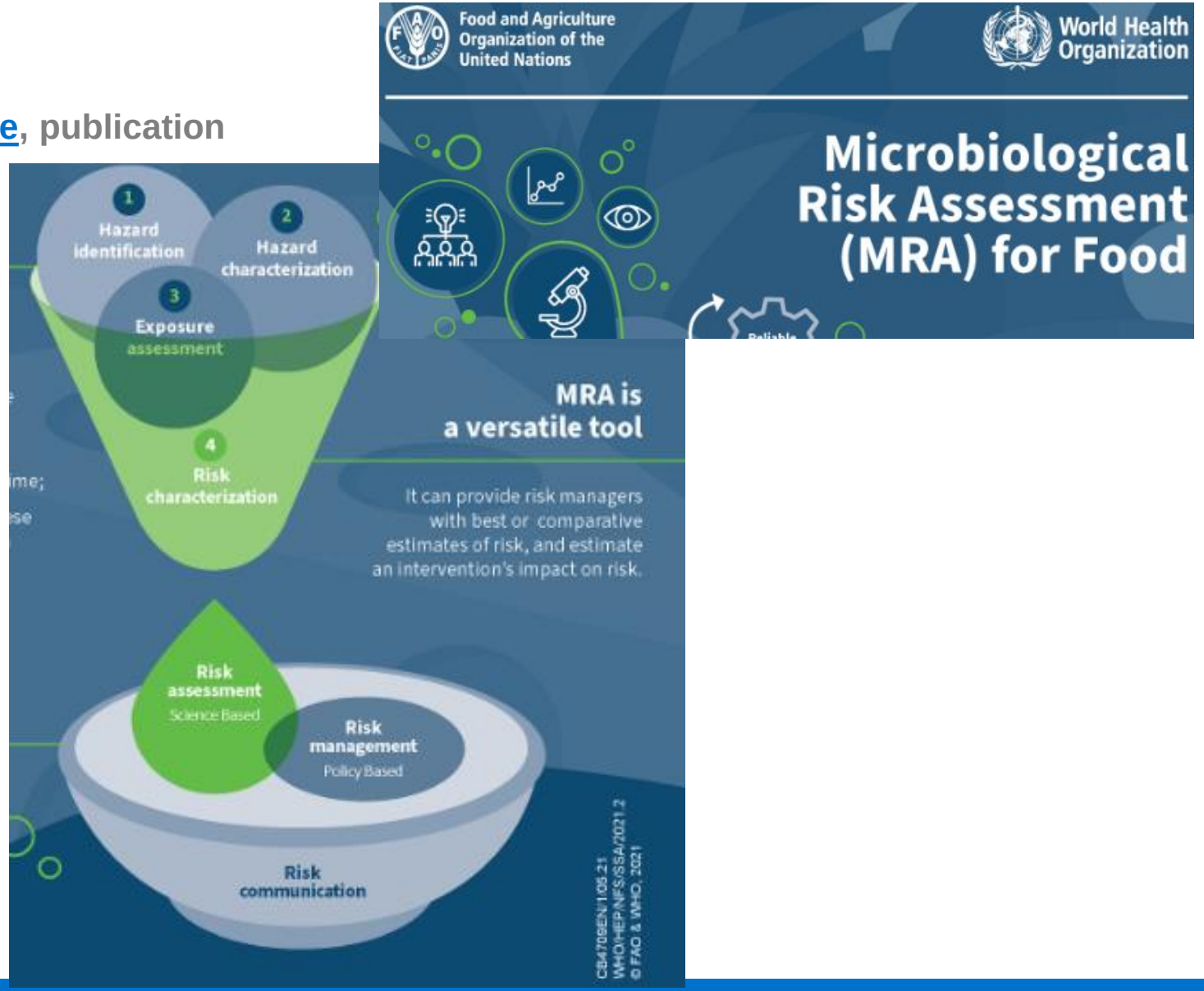
Conducted by registrants and validated by agencies

Risk **Assessment**, based on:
- Hazard characterization
- Exposure characterization

Qualitative, Semi-Quantitative, Quantitative (as needed)

Risk **Management** program
- Includes monitoring of mitigation

Risk **Communication**
- Producers and agencies



EXAMPLE – Microbiological risk assessment

[Microbiological Risk Assessment (MRA) in Food, FAO/WHO 2021]

RISK cuali/quantitative

HAZARD ID

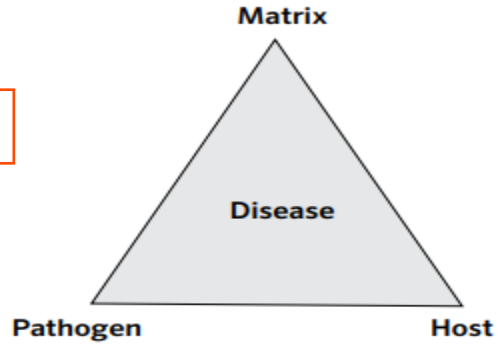


FIGURE 4. The epidemiology triangle (modified from Coleman and Marks, 1998)

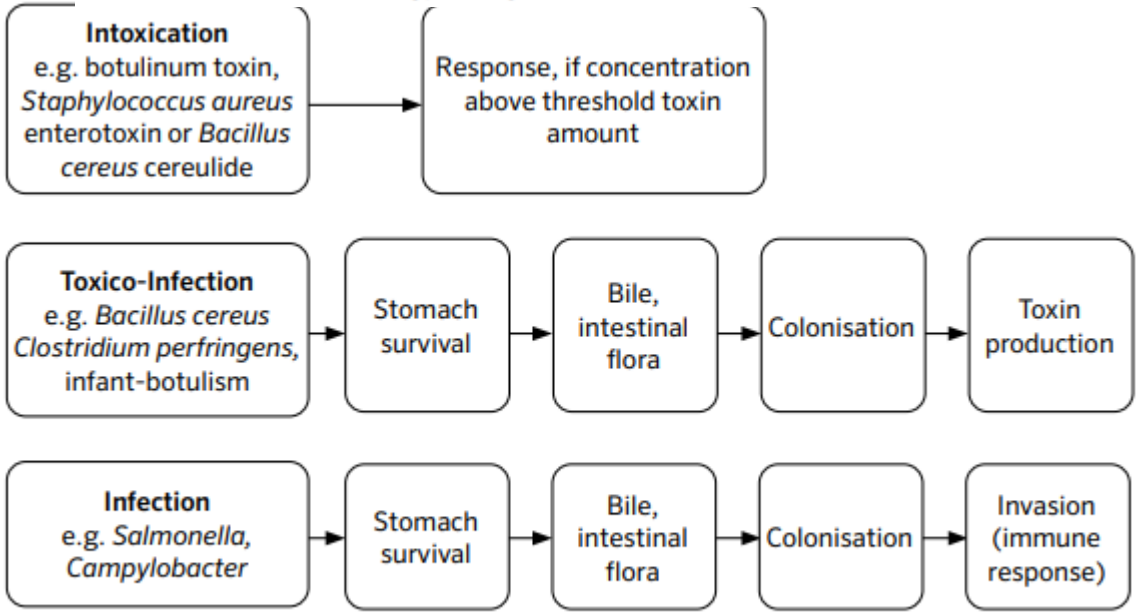


FIGURE 13. The major steps in the foodborne disease process

EXPOSURE ID

TABLE 8. A comparison of the process for computing the final risk estimate in risk characterization in quantitative and qualitative risk assessments. (Table adapted from Table 4 in Wooldridge (2008))

Stage	Quantitative risk assessment		Qualitative risk assessment	
	Probability	Computation	Probability	Computation
1	0.1		Low	
2	0.001	P(Stage 2) = P(Stage 1) x 0.001 = 0.0001	Very Low	P(Stage 1) x "Very Low" → Very Low (or lower)
3	0.5	P(Stage 3) = P(Stage 2) x 0.5 = 0.00005	Medium	P(Stage 2) x "Medium" → further reduction from very low
4	0.9	P(Stage 4) = P(Stage 3) x 0.9 = 0.000045	High	P(Stage 3) x "High" → further (small) reduction
Risk estimate		**0.000045**		**Very low (or lower)**

5. Conclusion & Recommendations

Conclusion	Recommendation
Biologicals can be registered and enforced as bio-pesticides, or bio-stimulants	MRL and import tolerances not needed but for exceptional cases
US requirements for channel of trade of biologicals	Consult USDA-APHIS & AMS, EPA, FDA
International trade standards for food exist for biologicals	Consult WTO, FAO, WHO, Codex
While MRL are not required, risk assessment for biologicals is required	Consult Codex guidelines, US EPA

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Thank you
Any questions?