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ASSESSMENT OF RESISTANCE DEVELOPMENT RISK IN THE FRAME OF BIOCIDAL PRODUCT AUTHORISATION AND ACTIVE SUBSTANCE APPROVAL

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1. French internal request on bacterial resistance to antimicrobial biocides

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1. Internal request on bacterial resistance to antimicrobial biocides

a. Background and purpose of the request

- Emerging bacterial resistance against different types of biocides (including disinfectants, antiseptics, preservatives and sterilants) (SCENIHR:https://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_q_012.pdf)

- 2016 (ANSES): internal request on bacterial resistance to antimicrobial biocides

  Report of French group of experts with complementary skills, between 2017 and 2019 in the frame of the EU Biocides regulation: https://www.anses.fr/en/system/files/BIOC2016SA0238EN.pdf

- Currently no guidelines on the assessment of unacceptable effects such as resistance => need approach for assessing the resistance phenomenon to biocide in order to help both the CA and the applicants meet the requirements laid down in Biocides regulation

Objective : propose methods for assessing the emergence of resistance/cross resistance, i.e. assessing the capacity, stability and level of any resistance that could be developed by bacteria following exposure to biocidal substances and products

b. Resistance in Biocide régulation (BPR) (EU) No 528/2012

- Recital 37

"When authorising biocidal products it is necessary to ensure that, when properly used for the purpose intended, they are sufficiently effective and have no unacceptable effect on the target organisms such as resistance, or, in the case of vertebrates, unnecessary suffering and pain."

- Article 19 (1b) (ii)

"The biocidal product has no unacceptable effects on the target organisms, in particular unacceptable resistance or cross-resistance or unnecessary suffering and pain for vertebrates"

c. French Working Group about approach for assessing biocide resistance

The French WG worked on the following items:

- Definitions related to resistance phenomena, main modes of action of biocides, and bacterial resistance mechanisms involved.
- Based on a literature review, current methodological approaches for assessing the ability of bacteria to develop resistance.

⇒ Proposal of an approach for assessing resistance

Focus on disinfectants and preservatives: 5 models used: Human hygiene, Surface treatment, Water treatment, Preservatives, Biofilms

⇒ Establishment of a decision tree

⇒ Strategy for managing the emergence of resistance

c. French Working Group about approach for assessing biocide resistance: Method (s) for assessing resistance

- Phase 1: Developing the experimental protocol adapted to the biocidal product (identifying as fully as possible the parameters and methods)
- Phase 2: Conducting tests
- Phase 3: Decision tree: Analysing results

c. French Working Group about approach for assessing biocide resistance: Method (s) for assessing resistance

Phase 1: Development of the experimental protocol

- Parameters related to the products (water quality, pH, use concentration, contact time, temperature, type of treatment/application…)
- Parameters related to microorganisms (relevance of species, inoculum size,…)
- Parameters related to the treated environment (soiling, type of surface,…)

c. French Working Group about approach for assessing biocide resistance: Method(s) for assessing resistance

Phase 2: Conducting tests

Two steps:

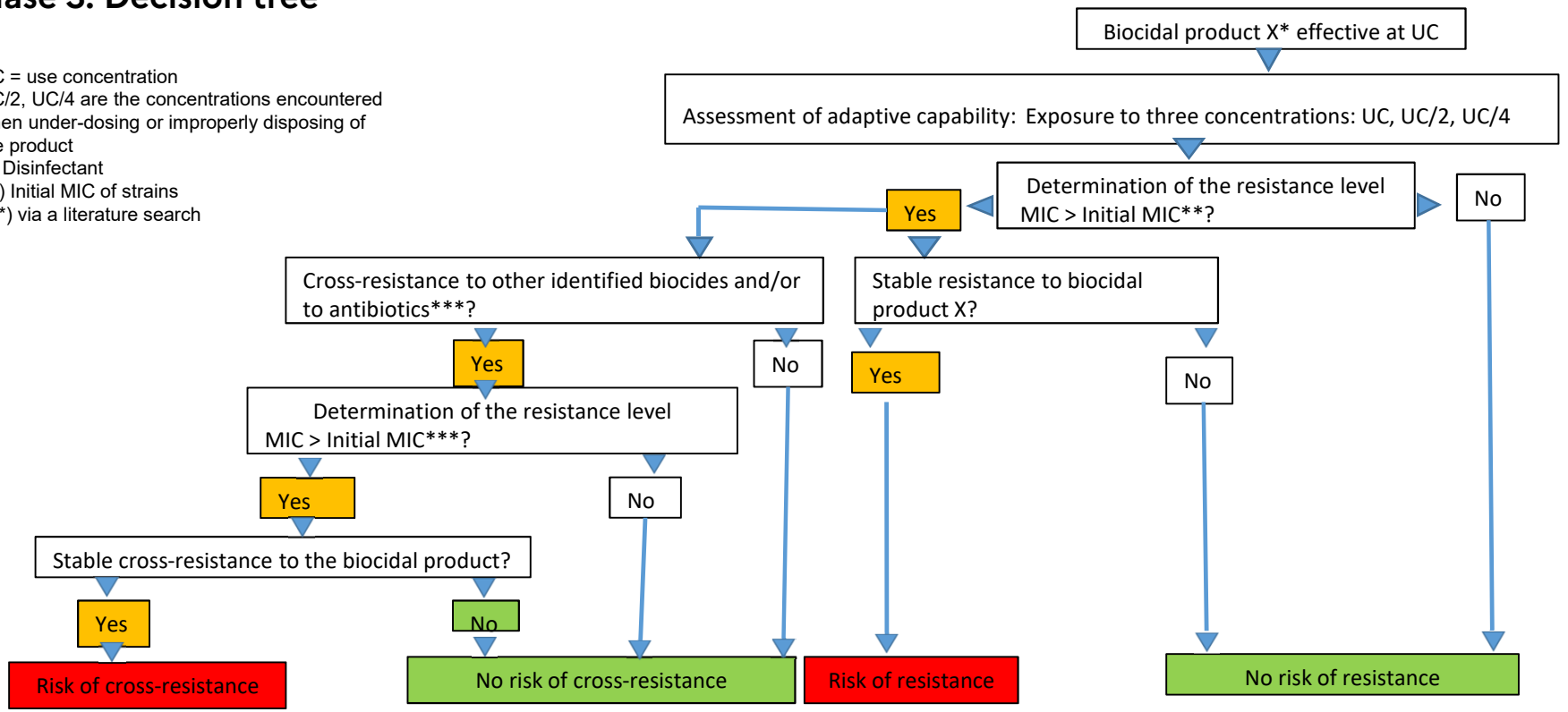
Before conducting test: Selection of the method(s) for assessing resistance (great diversity of methods described in scientific literature)

- Step1: exposure of bacteria to biocide
- Step2: if resistance is observed at step1, confirm or rule out the stability of this resistance

c. French Working Group about approach for assessing biocide resistance: Method(s) for assessing resistance

Phase 3: Decision tree

UC = use concentration
UC/2, UC/4 are the concentrations encountered when under-dosing or improperly disposing of the product
(*) Disinfectant
(**) Initial MIC of strains
(***) via a literature search



French Working Group about approach for assessing biocide resistance:
Strategy for managing the emergence resistance

Management measures applicable for all biocidal product types (PT)

- Instructions for use in Summary Product Characteristics (SPC) must mention absolute compliance with the conditions of use product
- Professional users should analyse causes of treatment ineffectiveness and inform authorisation holder (AH) should notify to the competent authority in the event of unexpected or adverse effects especially development resistance

French Working Group about approach for assessing biocide resistance:
Strategy for managing the emergence resistance

Post authorisation of Biocidal Product (BP) or post approval of Active Substance (AS) (field trials):

If / when risk resistance/cross-resistance observed in literature and/or laboratory testing => authorisation holders are requested to set additional experiments (laboratory tests) either post authorisation or post approval :

- If resistance/cross resistance is observed under conditions that **not comply with the BP use conditions**, the authorisation holder must inform users of these risks and advise them how best to comply BP conditions

- If resistance/cross resistance is observed under conditions that **comply with the BP use conditions**, it should be confirmed in the field:
  - Monitoring of micro-organisms population at several field sites from several weeks to several months
  - Characteristics of the strains present and their resistance can be investigated with the appropriate techniques

2. Proposal for resistance guidance

Objective of the Efficacy guidance at EU level

- Currently: no harmonised approach between Member states (MS), no guidance of resistance assessment

- Biocidal regulation: 2 levels of assessment => Active Substance approval and product authorisation

- In both reports assessment of Active Substance and Biocidal Product (CAR and PAR), section dedicated to « Occurrence of resistance and resistance management"

⇒Generally filled in with literature review (no key words harmonised for the literature research, no consensus on definitions, current state of the art without concrete risk mitigation measures if needed.)

⇒Part about resistance assessment in most of the cases neglected

Objective of the Efficacy guidance at EU level

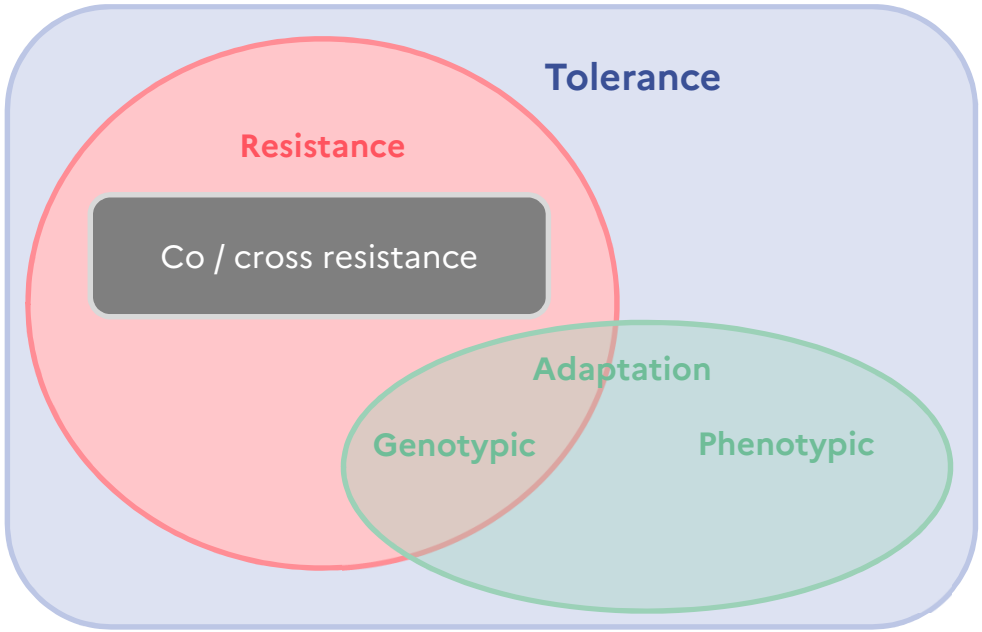
- **Proposal of draft guidance based on the French request with a tier approach :**

  - literature review
  - laboratory tests
  - field tests, if needed

- Common guidance for all PTs for Tiers Approach, literature review parts

- Starting discussions in 2021 (literature review, resistance definitions), 2022 (expected): tiered approach, parameters of laboratory tests

Definitions (WGIII-2021)

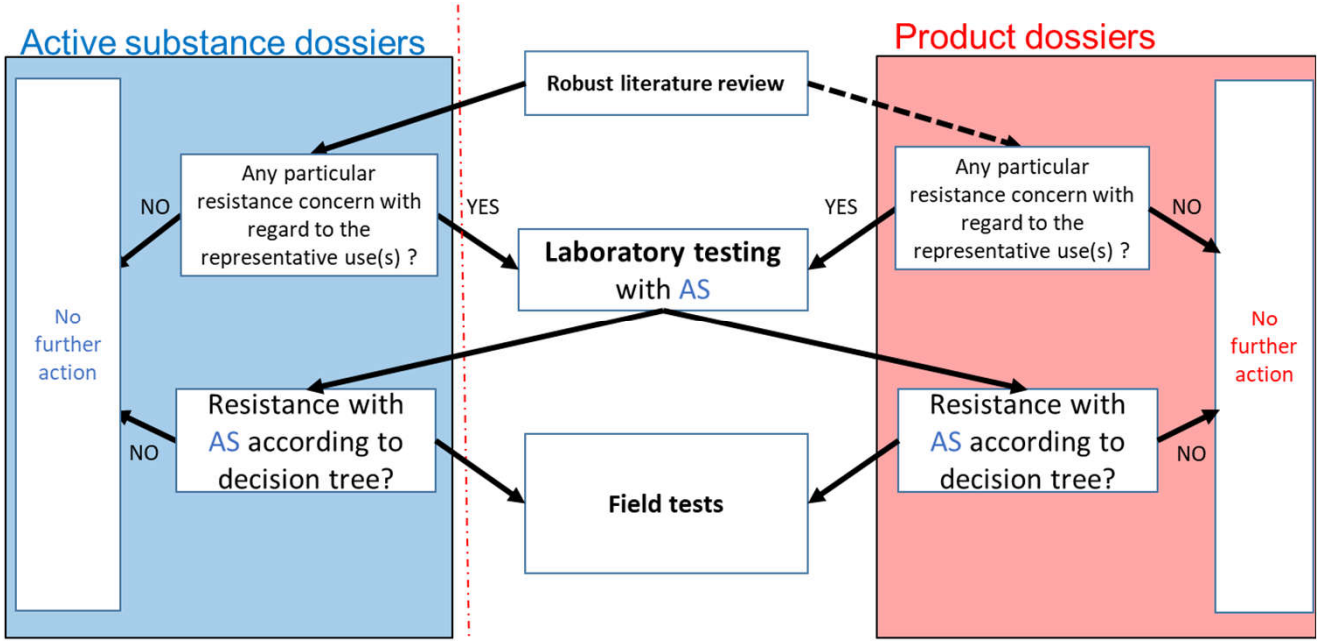


3. Next steps

Next steps (WG-2022- and probably after …)

Main points to be discussed at next efficacy WG in 2022

Tier approach: literature review, laboratory and field tests:
=> at which stage: approval /renewal AS - authorisation /renewal BP?



Next steps (WG-2022- and probably after …)

Main points to be discussed at next efficacy WG in 2022

Literature review: which criteria used to identify AS with potential risk of resistance?

Laboratory testing

- relevant tests depending of the product function: cidal, static effects
- choice of representative strains, number of strains, replication, media,
-cross-resistance with antibiotics: which antibiotics to test?
-concentrations in tests
-criteria resistance level

Field tests

=> development of protocols

….For more details, see :https://www.anses.fr/en/system/files/BIOC2016SA0238EN.pdf

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Thank you for your attention