Mandate "Azole-resistant Aspergillus": update

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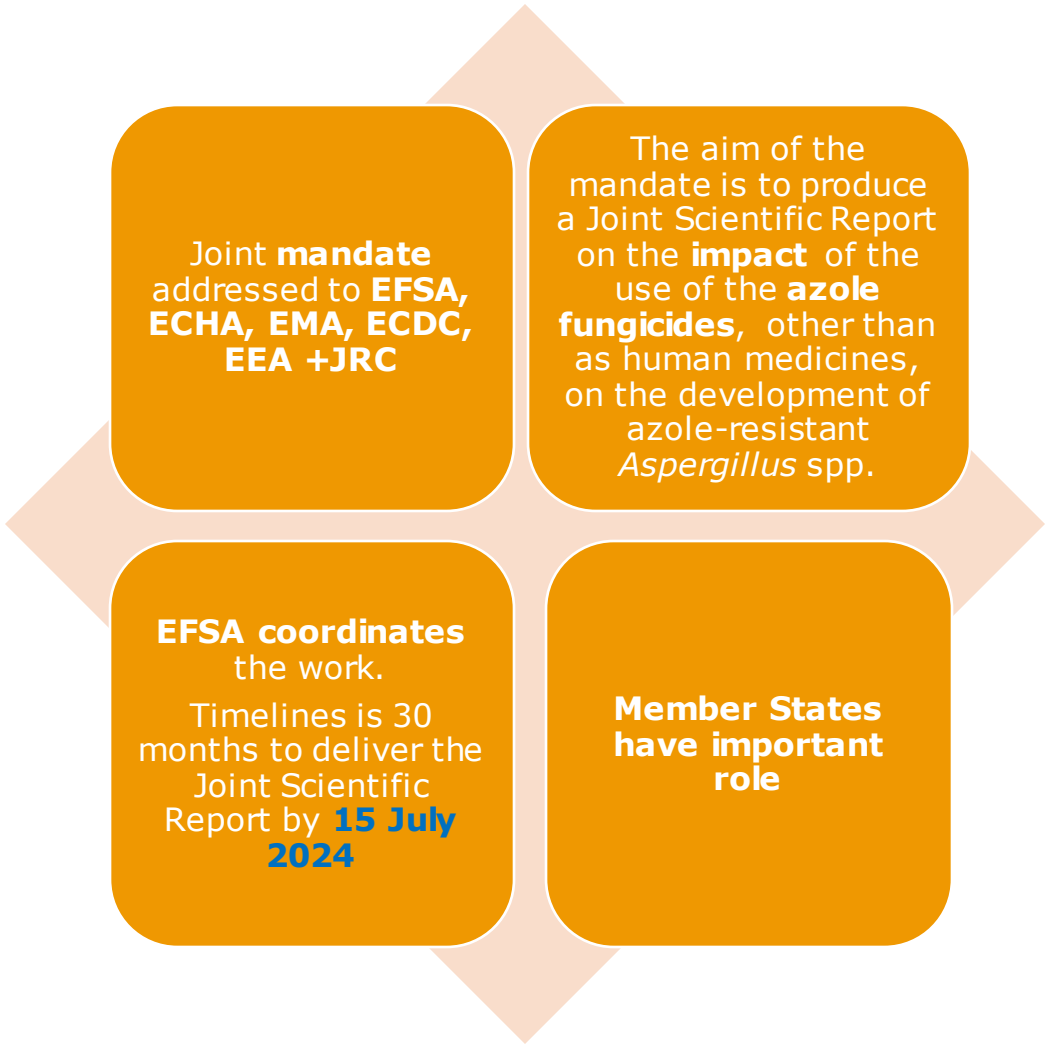
Background

- Many *Aspergillus* infections ("aspergillosis") are treated with azoles-based medicines with alternatives being limited.
- Resistance may develop during
  - treatment with azole medicines =>patient route
  - Develop in the environment => **environmental route**

  - There is growing evidence that *Aspergillus* spp. acquire **resistance mutations** when exposed to azoles in the environment!

The environmental route of resistance development could have serious implications leading to failure of azole therapy, particularly in patients with invasive aspergillosis.

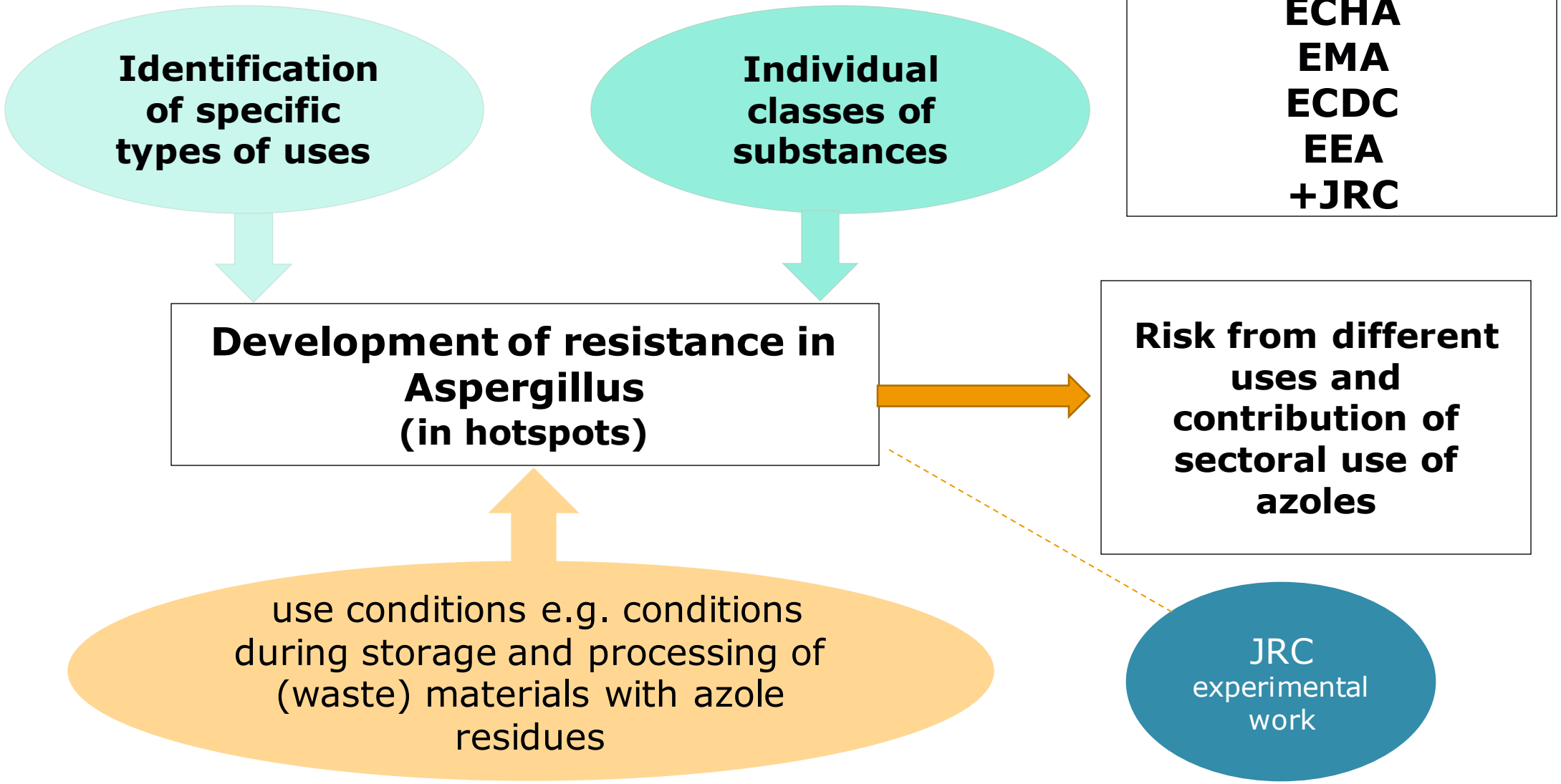
Impact of azole fungicides on the development of azole-resistant *Aspergillus spp*.



ToRs in the mandate

1. Uses
2. Use -> resistance in environment
3. Resistance in environment -> humans
4. Assessing risk
5. Risk factors in hotspots (use, storage conditions, etc.)
6. Prevention and control measures
7. Studies by applicants
8. Uncertainties and data gaps

Development of azoles resistance in hotspots

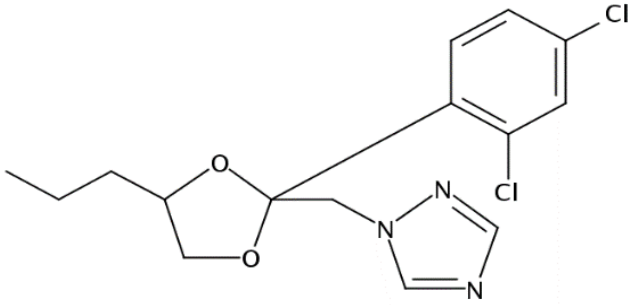


ToR1 – Chemical families

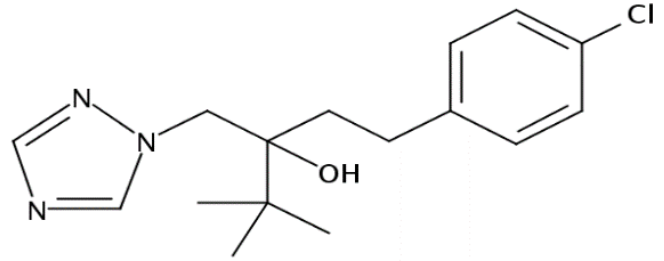
4 Regulatory regimes: PPP, biocidal products, industrial chemicals, veterinary products

- Known azoles active substances - causing resistance of *Aspergillus fumigatus - example*

  - **PROPICONAZOLE, EC: 262-104-4, CAS: 60207-90-1**
    - 1-[[2-(2,4-Dichlorophenyl)-4-propyl-1,3- dioxolan-2-yl] methyl]-1H-1,2,4-triazole (Propiconazole)



  - **TEBUCONAZOLE, EC: 403-640-2, CAS: 107534-96-3**
    - 1-(4-Chlorophenyl)-4,4-dimethyl-3-(1,2,4- triazol-1-ylmethyl)pentan-3-ol



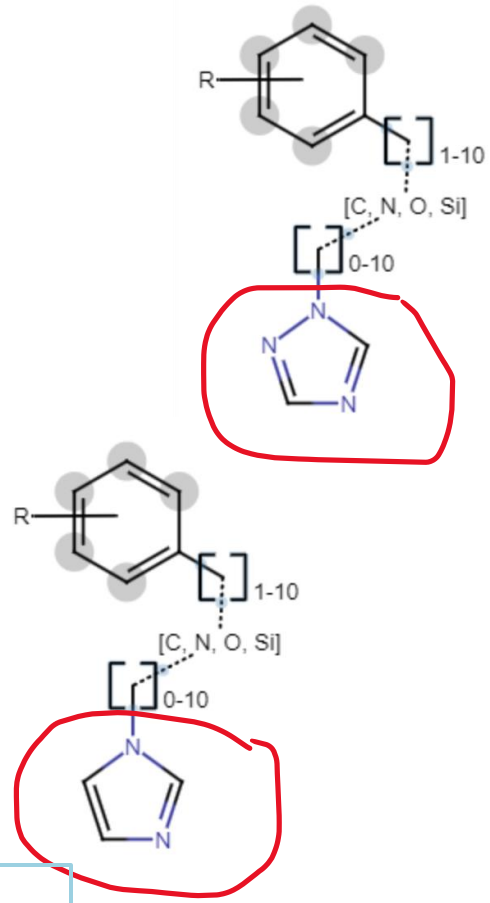
The inter-agency group has developed an azole inventory

Complete list of substances

- Azoles fungicides substance List has been finalised

- 131 rows in the dataset ("substances")
  - main substances from the 2 main groups – imidazoles and triazoles
  - salts
  - isomers
  - same substance with different numerical identifiers

  - Different regulatory statuses marked for each substance



The list consists of substances from the 2 main groups – **imidazoles** and **triazoles** and also 9 outliers. Only around 50-60 substances however are really relevant for collection of information. Also substances which are not anymore "authorised/approved" are on this list if approval expired after 2010.

Collection of data : Azoles fungicides uses

Member States will be requested to give feedback to EFSA/ECHA *(collection of data on the uses part of ToR)*

- Provide details about the **use of azole fungicides**, other than as human medicines, in the EU/EEA giving information about:
  - the types of use,
  - the current and trend in quantities used and
  - as much detail as possible on geographical variation.

Member States to reply to a SURVEY/QUESTIONNAIRE that will be circulated by EFSA likely on the uses of azole fungicides as PPP

Questionnaire to MS about quantities

- **EU Survey** will be used
- Same format as **EUROSTAT** questionnaire

35 substances

  - ✓BPR, PPP, VMP
  - ✓Not REACH as ECHA has data about quantities

- Collect annual data about quantities from 2010 – 2022
- Exact questions and instructions will be agreed in ToR1
- Each Agency will collect information from MSCAs on the "relevant" substances from the finished "list of azole fungicides"

- **Agree on what data to collect (October-December 22)**
- **Survey (to be launched in Jan 2023)**
- Collection of data **(by end of March 2023)**
- Summarising data **(By end of 2023)**

ToR 2- Causative link between the use of azole fungicide and development of azole-resistant Aspergillus species

- To respond to the request ECDC performed a **systematic literature search** aiming to identify **azole resistance mechanisms** described in the human, agriculture and environmental domains.
- The results on search strategy identified **2357** records. Abstracts screened and included: ca 200
- Next steps will be: Full text screening, final conclusion on the number of **articles** to be included

  ✓ Final outcome will be a **matrix** of **azole resistance mechanisms** identified across the three domains. The presence of the same resistance mechanisms in the agriculture and/or environmental domain as well as in the human domain (azole-naïve humans) would suggest a **correlation between** the use of azole fungicides, other than as human medicines and azole-resistant Aspergillus species infections in humans.

  ✓ This will be the case also for substance not included in the questionnaire because **not approved** in the EU but for which information shows correlation with resistance, this could be included in the final text for completeness.

…Work in progress!

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