CropLife EUROPE

Experiences with cumulative risk assessments in the agrochemical industry and views

Virtual Conference

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NVT Risk Assessment Section "Mixture Toxicity", 5th October 2021

European Approach (I)

Discussions / Societal concerns
Studies and publications
Literature Reviews
European Projects (under Horizon 2020 framework)

Possible relevant matrices/exposure scenarios

Products

Applications

Possible relevant regulatory areas

EC 1107/2009

European Commission

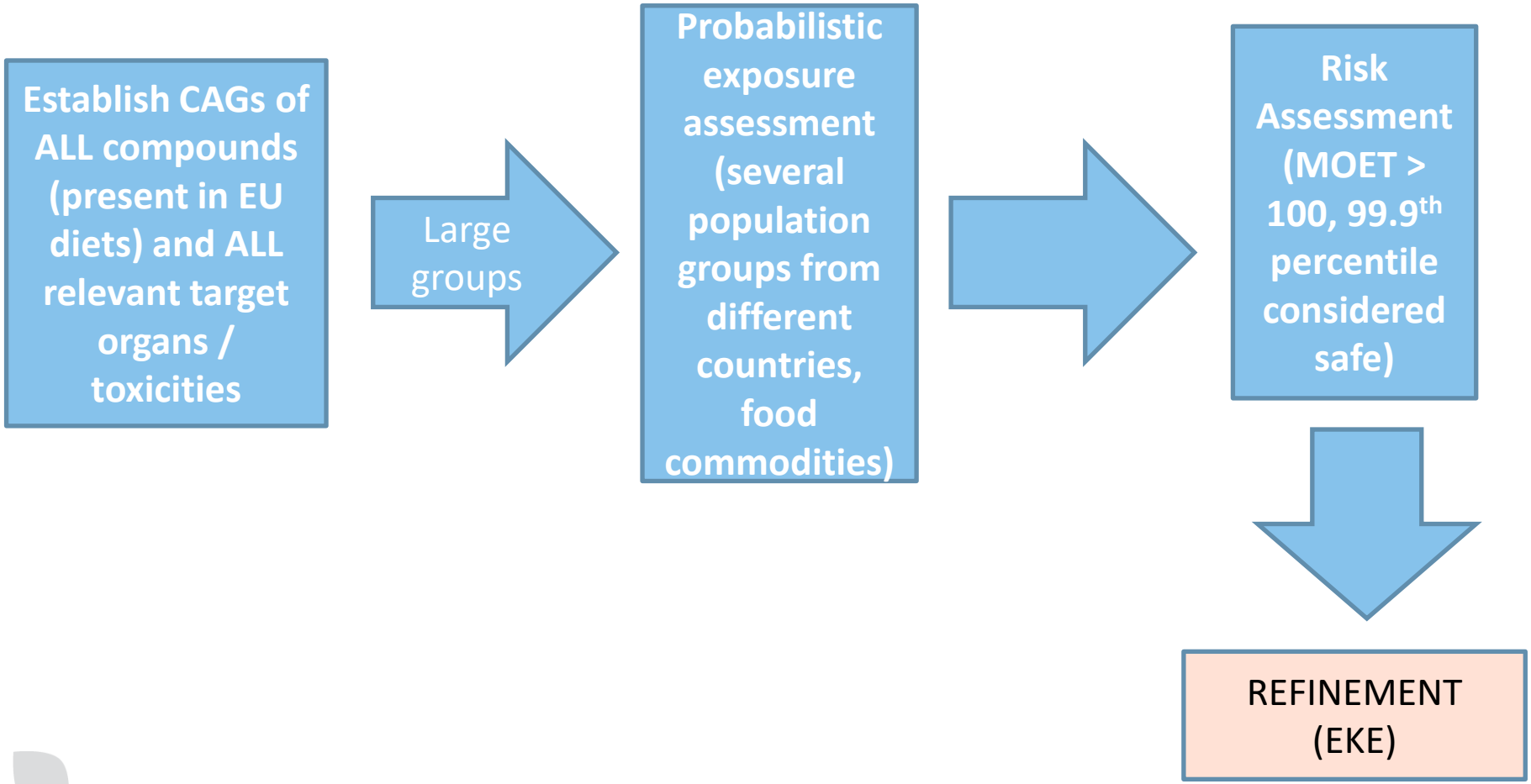
EC 396/2005

Authorization of plant protection Products in Europe

Maximum residue levels of Pesticides in food & feed

European Approach (II)

Cumulative dietary risk assessment pesticides



CAG – Cumulative assessment group
MOET – Total Margin Of Exposure
EKE – Expert Knowledge Elicitation

Work done in the field of cumulative dietary risk assessments (2013 – 2021)

2009: 1st tryout: Azoles

2013 – 2019: Development of CAGs

2018-2020: Probabilistic retrospective CRAs

Prospective assessments

Cumulative Assessment Groups (CAGs)

- 2 chronic thyroid groups
- 4 acute nervous system groups
- 5 chronic nervous system groups

Retrospective Cumulative Risk Assessments (CRAs)

- Chronic hypothyroidism
- Acute motor division and acute AChE inhibition
- Chronic AChE inhibition

Retrospective Cumulative Risk Assessment

- In all cases, „cumulative exposure does not reach the thresholds for regulatory consideration for all the population groups considered.“
- In the worst-case scenarios, the impact of uncertainties has been identified and exposures and hazards have been refined (Expert Knowledge Elicitation (EKE) process).

Other learnings from retrospective CRAs

- Cumulative risk is driven by only few substances and commodities
- Acute cumulative risks is especially driven by non-compliant samples (i.e. showing MRL exceedances)
- Exposure refinement difficult as data are sometimes lacking (e.g. processing factors, use frequencies)
- Hazard refinements possible by deriving Benchmark Doses (BMDs)

EU Chemicals Strategy for Sustainability (CSS)

14th Oct. 2020

One relevant element of the CSS: **Assessment of mixtures**

combined exposure to multiple chemicals from different sources and over time[49]. For people, the combination effects of chemicals may intensify in closed environments. Some pieces of legislation[50] require to assess the cumulative exposure to the same chemical from different sources. Explicit requirements to take into account the impact of **unintentional mixtures** is generally lacking, currently existing for the protection of workers[51]. The pesticides and biocides legislation require to consider cumulative and synergistic effects[52]. For pesticides, progress has been made in developing a targeted methodology, and work will be accelerated so that existing provisions can be fully implemented[53].

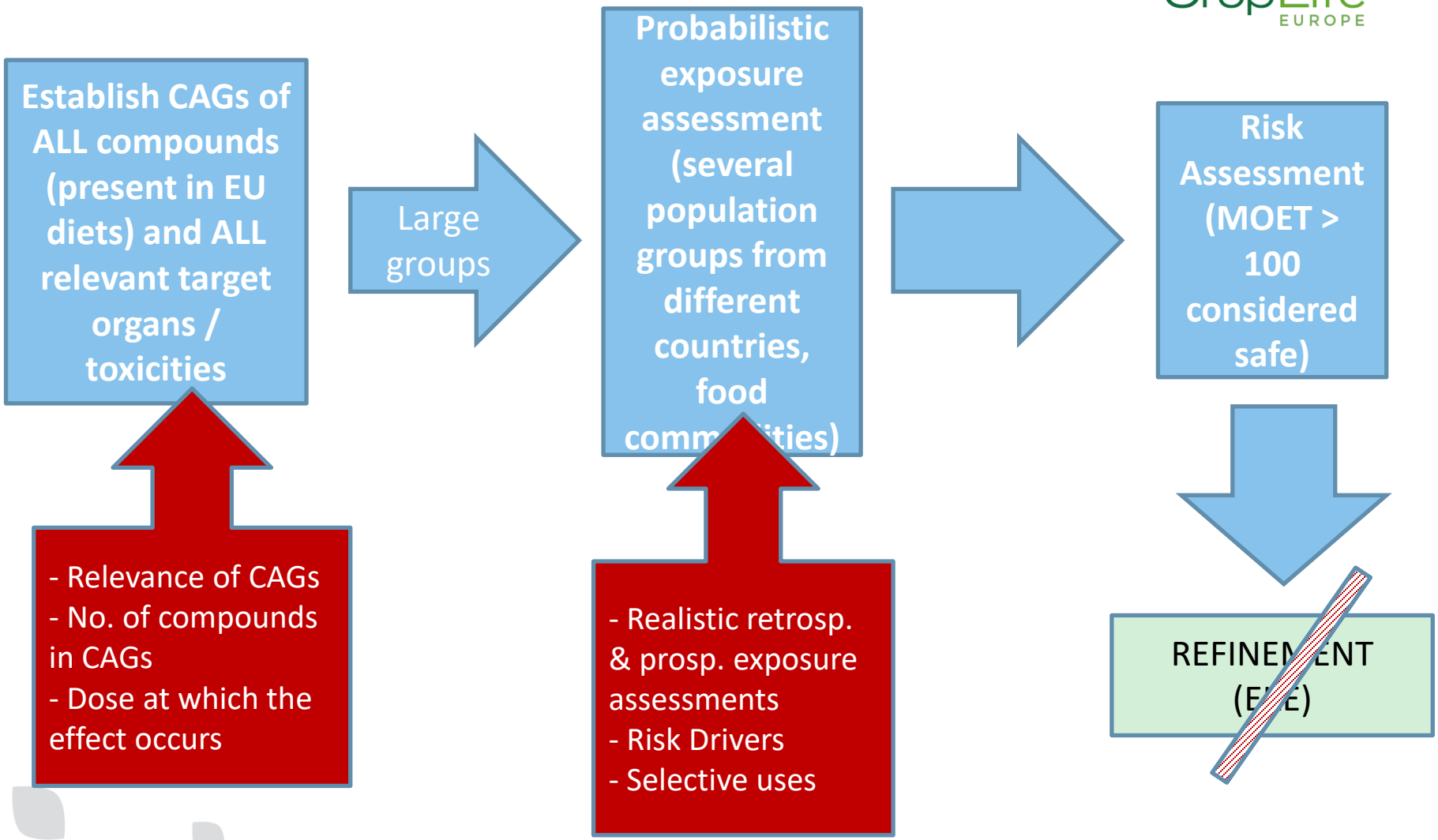
EFSA/DG Sante Action Plan

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Safety of the Food Chain
Pesticides and Biocides

- **Prioritization and elaboration of new cumulative assessment groups (CAGs)**
- **Retrospective cumulative risk assessments**
- **Prospective cumulative risk assessments**
- **Integration of non-dietary exposure**

Prioritization is needed



CAG – Cumulative assessment group
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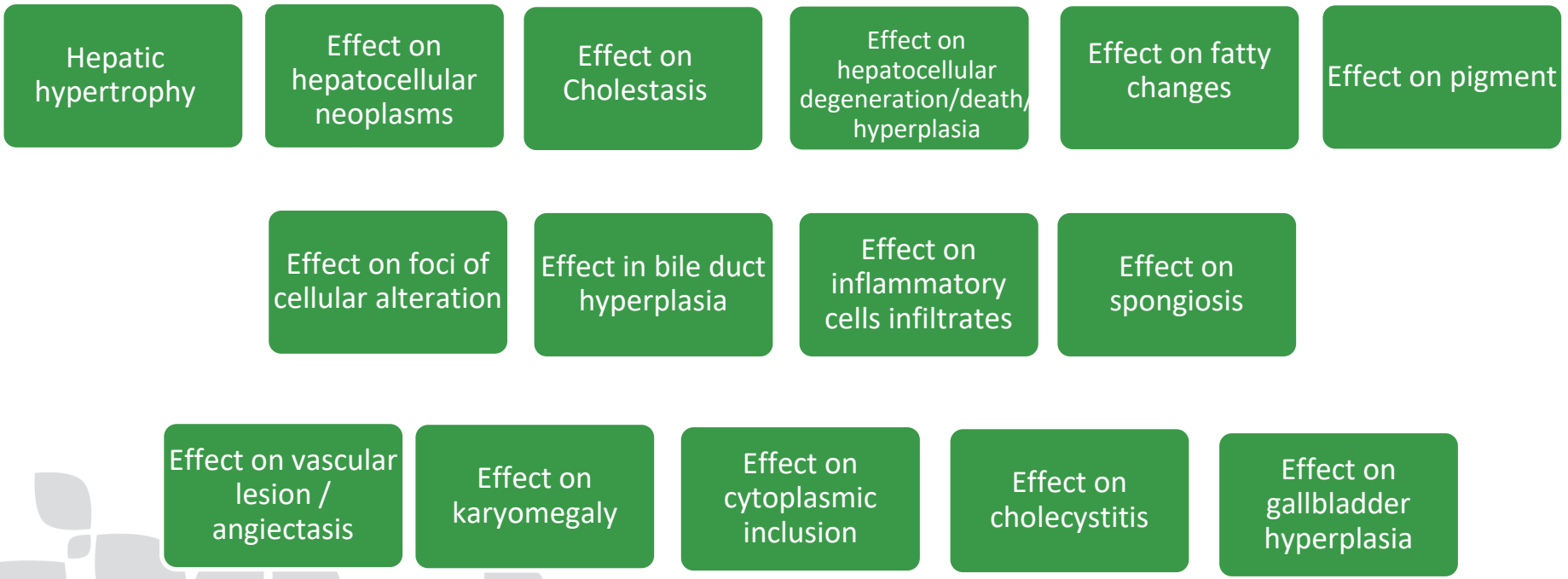
External Scientific Report, 2021 (RIVM): Impact on Prioritization methods

Establish relevant groups – e.g. liver

- **Consider known and common pathophysiology of toxic lesions**
  - Primary lesions (direct consequence of chemical interaction)
  - Secondary lesions (consequence of/or arising from a direct lesion)



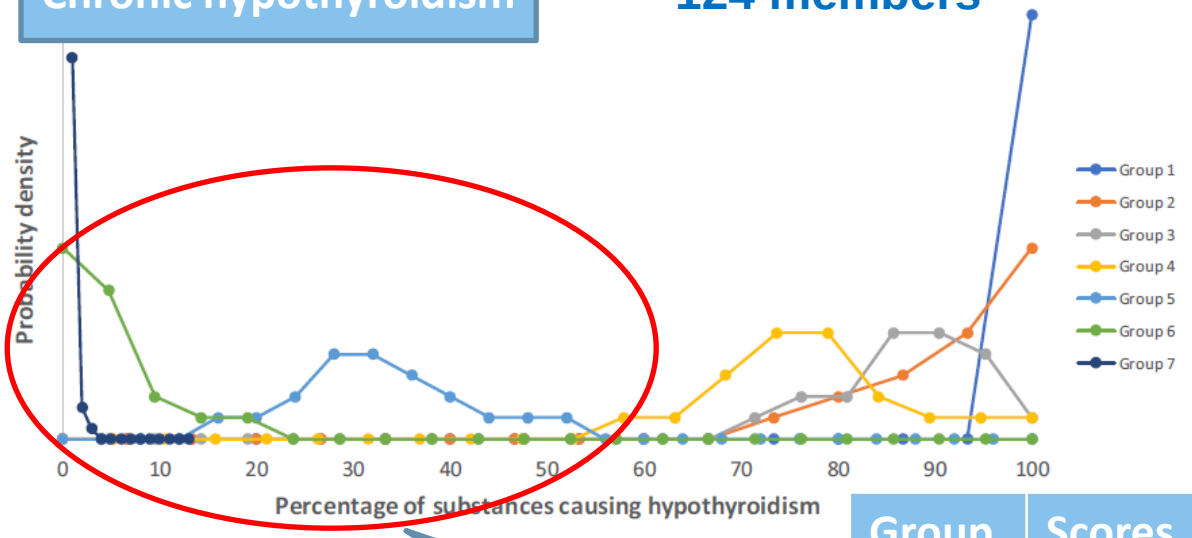
Ref.: External Scientifc Report (2016) CAGs for effects on liver

Published under: Foster et al., 2020

Uncertainties in assigning substances to CAGs – thyroid

Chronic hypothyroidism

124 members



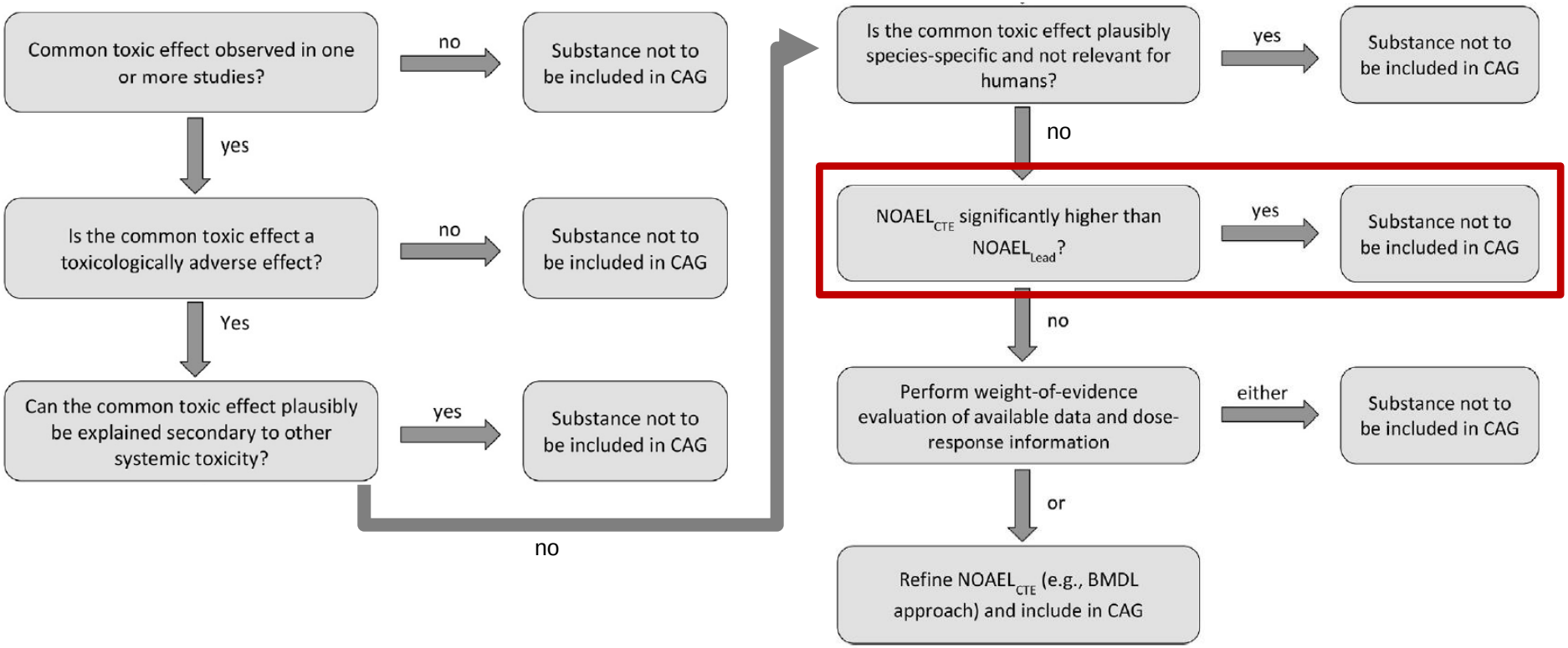
Scores: Measure for strength of the WoE

Exclude from the group?

Group	Scores	# of AIs
1	1502.56 – 2791.19	7
2	461.99 – 1154.98	11
3	176.63 – 294.89	27
4	73.09 – 122.02	22
5	13.09 – 54.44	*24*
6	6.04 – 9.75	*18*
7	1.38 – 4.03	*23*

Ref.: EFSA (2019) CAGs for effects on thyroid

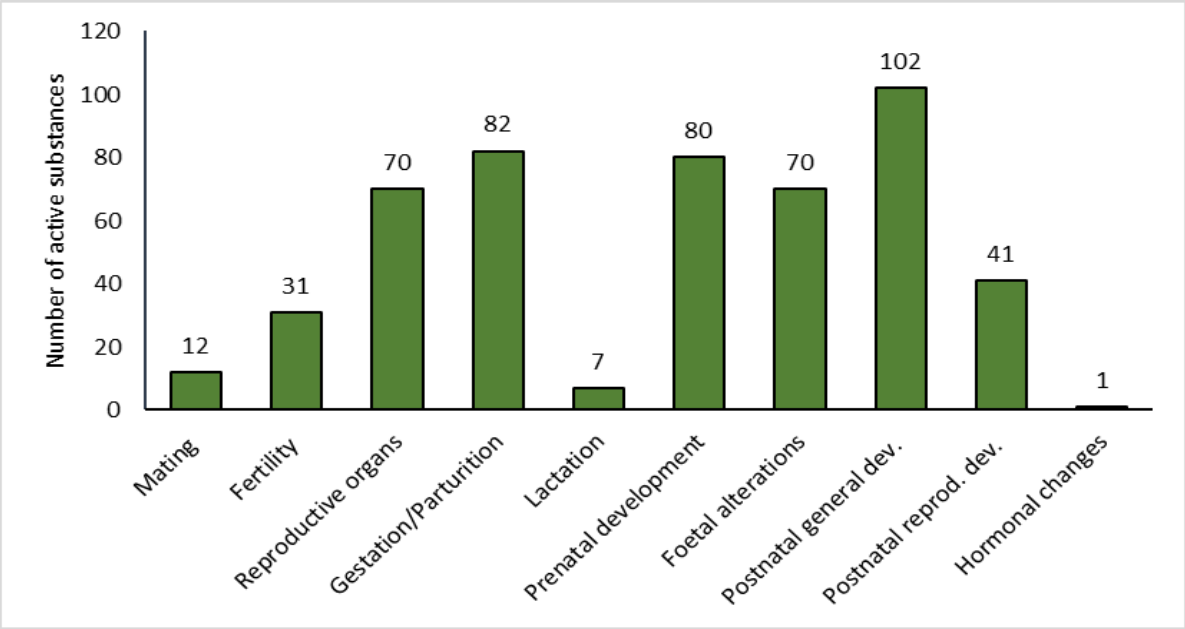
Apply criteria more stringently - proposed flow scheme



NOAEL$_{CTE}$ – lowest NOAEL for the Common Toxic Effect
****NOAEL$_{Lead}$ – NOAEL used for ADI, ARfD**

Colnot et al., 2020

Reproduction & Development:
Avoid redundancies and apply stringent Criteria

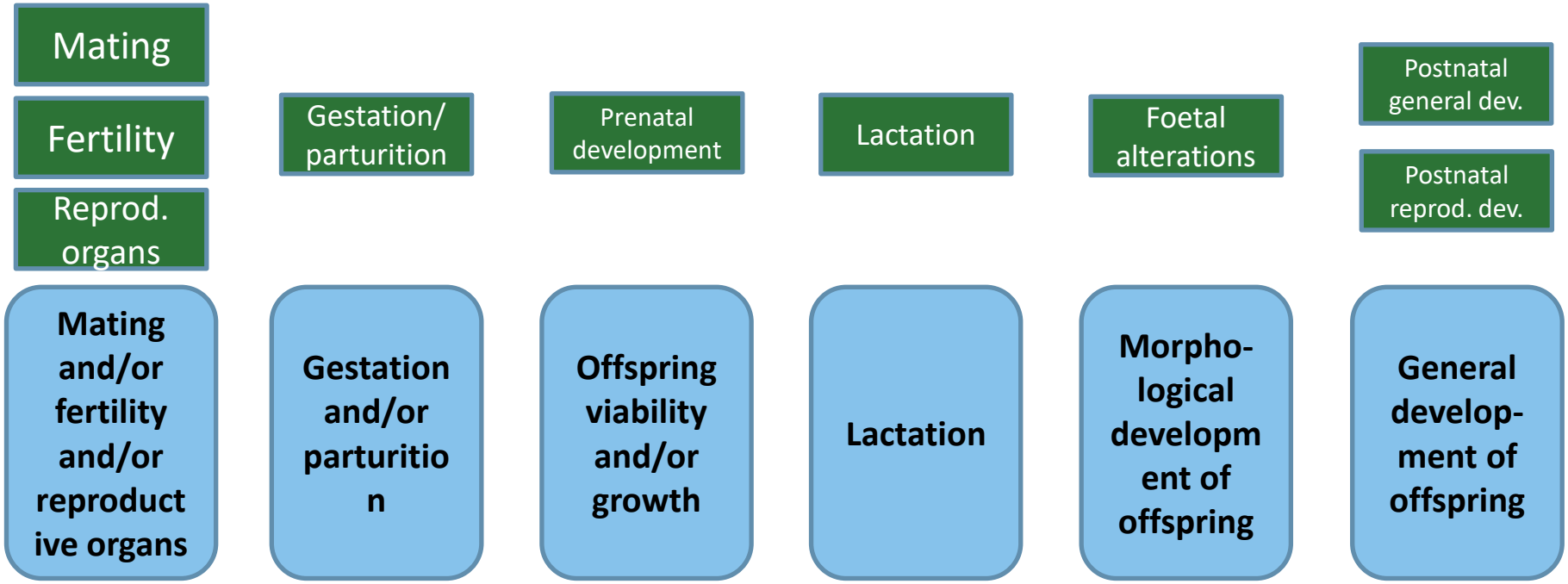


124 /129 compounds have been assessed to belong to at least one CAG

Ref.: External Scientific Report (2016) CAGs for effects on reproduction & development

CropLife Europe Assessment:
Assignment of compounds to CAGs is (in parts) redundant
CAGs could be combined
No stringent application of classification criteria
Suggest to compare with Authority decision on C & L

Possibly more plausible groups



- Majority of reproduction/developmental effects occur at doses >> overall LOAELs
- Focus on lead toxicity (common toxic effect = lead toxicity) probably more efficient

Moxon et al., submitted 2021

Avoid redundancies and apply stringent (C&L) Criteria

Substances with a harmonised classification for reproductive toxicity			
8-Hydroxyquinoline Cat. 1B (H360D)	Pinoxaden Cat. 2 (H361d)	Spirotetramat Cat. 2 (H361fd)	Tembotrione Cat. 2 (H361d)
Substances with a RAC Opinion proposing a classification for reproductive toxicity			
Fluxapyroxad Lact. (H362)	Ipconazole Cat. 1B (H360D)	Isopyrazam Cat. 1B (H360D)	Metaflumizone Cat. 2 (H361fd)
Halosulfuron methyl Cat. 1B (H360D)			
Substances with an EFSA proposed classification for reproductive toxicity			
Flubendiamide Cat. 2 (H361d) Lact. (H362)	Indolylbutyric acid Cat. 2 (H361fd)	Metam (including potassium & sodium) Cat. 2 (H361d)	Spinetoram Cat. 2 (H361fd)
Substances approved without classification for reproductive toxicity			
Acequinocyl	Chromafenozide	Mandipropamid	Pyriofenone
Acrinathrin	Cyantraniliprole	Meptyldinocap	Pyroxsulam
Ametoctradin	Cyflumetofen	Metalaxyl	Sedaxane
Aminopyralid	Emamectin benzoate	Metobromuron	Spinetoram
Amisulbrom	Fenpyrazamine	Penflufen	Spiromesifen
Azadirachtin	Fluopyram	Penthiopyrad	Sulfoxaflor
Benalaxyl-M	Iron sulphate	Pyridalyl	Thiencarbazone
Bixafen			Valifenalate

Table 4: Approved active substances (from the total of 129 considered by ANSES) and status on classification for reproductive toxicity (EU pesticides database, accessed 21 January 2021) or proposed classification by ECHA RAC or EFSA (Supplementary Table 1)

All listed AIs were proposed for grouping in ≥ 1 $CAG_{reproduction\&development}$

Moxon et al., submitted 2021

Hazard-based prioritization criteria for retrospective scenarios - ideas

- Generate tables with individual hazard quotients
- Generate a list with main target organ toxicity (driving reference dose setting ADI & ARfD)
- Identify the quotients between common toxic effect and lead toxicity
- Establish LOAEL / bioavailability combinations
- Suggest to use more stringent criteria to assign substances to CAGs, which would make refinement using EKE techniques unnecessary

Exposure-based prioritization criteria for retrospective scenarios

- **Identify main „exposure drivers“**
- **Develop a matrix to identify major likely co-exposures**
  - Multiple residues
  - Combine with consumption data
- **Focus on major crops/uses**
- **Exempt substances with no / isolated residue findings**
- **Need for realistic assumptions to handle residues < LOQ**
- **EKE Methodology**
  - It is suggested to estimate exposure using realistic assumptions, which would make refinement using EKE techniques unnecessary

Prospective scenarios – CLE views

- **Exposure data**
  - In the absence of monitoring data, exposure likely to be modelled using overconservative and unrealistic exposure/concentration data
  - A need for realistic refinements in place of worse-case defaults
  - Handling of LoQs, processing factors, modelling of field trials data
- **How can more realistic assessments be done?**
  - Consideration of expected maximum market share (use frequencies) of the active substance (percentage crop treated)

Prospective scenarios – CLE views

Emergency use

- Exemptions/deferred assessment for emergency authorisations due to the urgent nature of the request

Prioritization

- Focus on major crops/uses
- Limited value in repeating assessment for each extension of use for minor crops/uses
- Use of more simplistic approaches to identify exposure / risk drivers as tool to prioritize need?

Criteria for prospective assessments

- **Monitoring data for „background“ exposure**
  - 3 years cycle of concentration data
  - Exclude non-compliant residue events where risk management action taken as a result of retrospective assessment
  - Exclude data where substances are no longer authorised (except where ITs or CXLs are in place)
  - We need to make sure, that the registration of modern low-risk AIs is not prevented by uncertainties around „old“ compounds
- **Clarification on the protection goals**

IT – Import Tolerance
CXL – Codex MRLs

RIVM Report (each 15 case studies)

acute motor division & chronic hypothyroidism

- **Tiered approach is proposed**
  - Tier 0 (all deterministic); Tier I (deterministic plus background probabilistic)
- **Tier II assessment**
  - MRL scenario
  - GAP scenario (exposure to focal commodity treated with focal substance at the critical GAP)
  - Actual scenario (more realistic): same as above but considering an estimated use frequency (minimum of 20%)
- **Application of a trigger value (e.g. %age of HBGV)?**
- **Final criteria to be agreed by the EU Commission (SCoPAFF) – Risk Management**

Ref.: External Scientific Report (2021)
Proposed prospective scenarios

HBGV – Health-based Guidance Value

Conclusions

- Establish new CAGs only on relevant target (organ) toxicity
- Apply more stringent criteria to substances for inclusion into CAGs
- Consider to group only compounds: common target effect = lead toxicity
- Substances with low individual hazard quotients could be exempted from CRAs
- Focus on major crops/uses
- Use most realistic exposure estimates (e.g. use frequencies, processing factors)
- Ensure existing tools are available to industry and to all interested parties (and made more transparent) to calculate background exposures
- **We suggest to be more stringent/realistic in the beginning, which might make extensive refinement (EKE) unnecessary**

Future challenges

- **Aggregate exposures**
  - Lack of non-dietary exposure data
  - Conservativeness of modelled exposure data
- **Open data bases**
  - Access to relevant EU consumption data
  - Integration of company/industry data (see GFL)
  - Access to monitoring/concentration data (background exposure data) available in a suitably detailed format
- **Risk Management Expert Group needs to finally decide on scope and criteria**
- **Risk management options/decisions when exceedances of cumulative risks are determined**

Statement

- **The use of hazard and exposure data is a better way to identify critical (human) scenarios, than applying generic mixture assessment factors.**