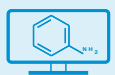


# Cumulative dietary risk assessment

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Stephanie Melching-Kollmuss

GPTS Advanced Course “Mixture toxicology”  
17<sup>th</sup> March 2026



**Toxicology**  
safe use — safe people

 **BASF**

We create chemistry

# Concepts for conducting Assessment of Mixtures

- Published by Meek et al., 2011

Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework<sup>☆</sup>

M.E. (Bette) Meek<sup>a</sup>, Alan R. Boobis<sup>b</sup>, Kevin M. Crofton<sup>c</sup>, Gerhard Heinemeyer<sup>d</sup>, Marcel Van Raaij<sup>e</sup>, Carolyn Vickers<sup>f,\*</sup>

<sup>a</sup>McLaughlin Centre, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada

<sup>b</sup>Department of Experimental Medicine and Toxicology, Division of Investigative Science, Imperial College London, London, England, United Kingdom

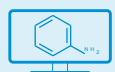
<sup>c</sup>National Health and Environmental Effects Research Laboratory, Office of Research and Development, Environmental Protection Agency, Research Triangle Park, NC, USA

<sup>d</sup>Federal Institute for Risk Assessment (BfR), Berlin, Germany

<sup>e</sup>National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands

<sup>f</sup>International Programme on Chemical Safety, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland

- Principles can be applied in very different contexts
- And regulatory frameworks

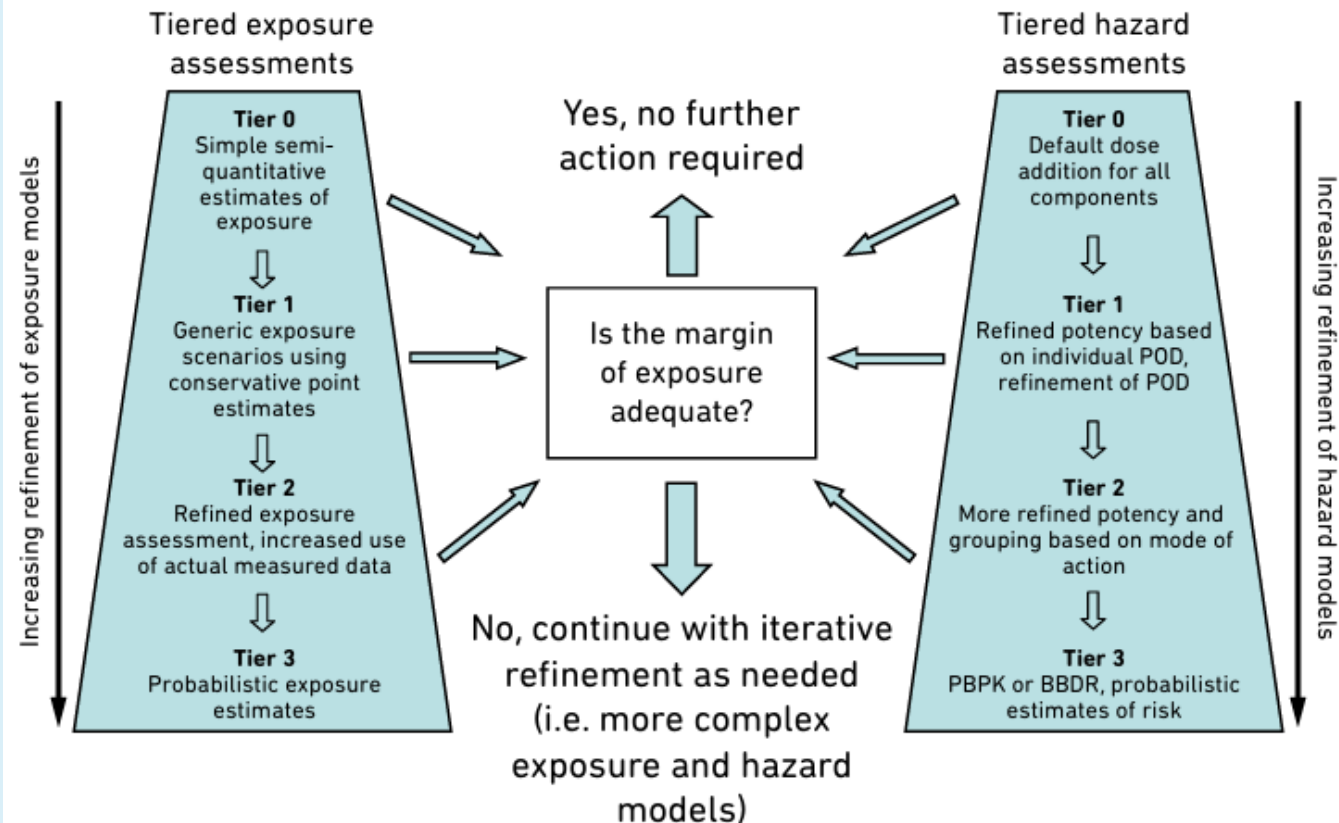


## Problem Formulation for Combined Exposure Assessment

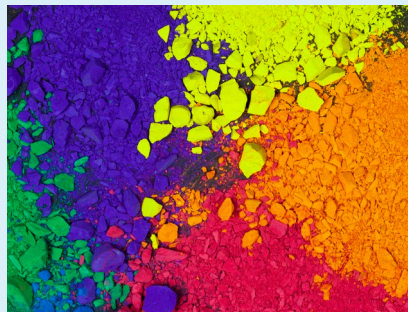
- What is the nature of exposure?
- Is exposure likely, taking into account the context?
- Is there a likelihood of co-exposure within a relevant timeframe?
- What is the rationale for considering compounds in an assessment group?



## Example Tiered Exposure and Hazard Considerations: Mixture or Component Based



# The European Approach



Discussions / Societal concerns  
Studies and publications  
Literature Reviews (combinations of „low dose exposures“  
„Something from nothing“)  
European Projects (Acropolis, Euromix, EDCmixrisk,...)

## Possibly relevant exposure scenarios, e.g.



Water



Food



Agricultural applications

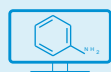
## Possibly relevant regulatory areas

### 1107/2009 Pesticide Regulation

REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL  
of 21 October 2009  
concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC

### 396/2005 MRL - Regulation

REGULATION (EC) No 396/2005 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL  
of 23 February 2005  
on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC  
(Text with EEA relevance)  
(OJ L 70, 16.3.2005, p. 1)



# Grouping Approach proposed / conducted by EFSA

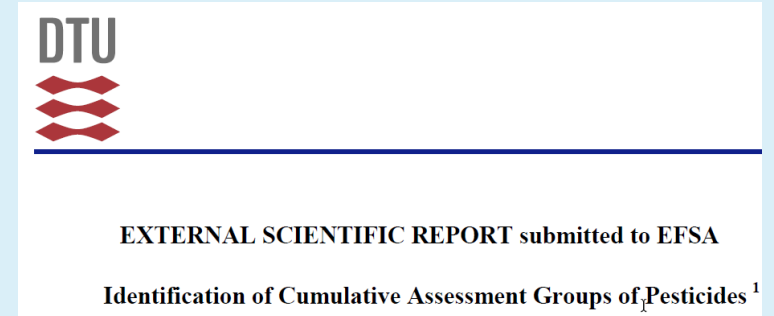
Huge data collection  
DTU, 2012

- CAG level 1: Toxicological **target organ**
- CAG level 2: **Common** specific phenomenological **effect**

---

- CAG level 3: Common mode of action
- CAG level 4: Common mechanism of action

Rarely data  
available



Chemicals with  
common target organ  
toxicity (any effects in  
any study, dose level  
or species)

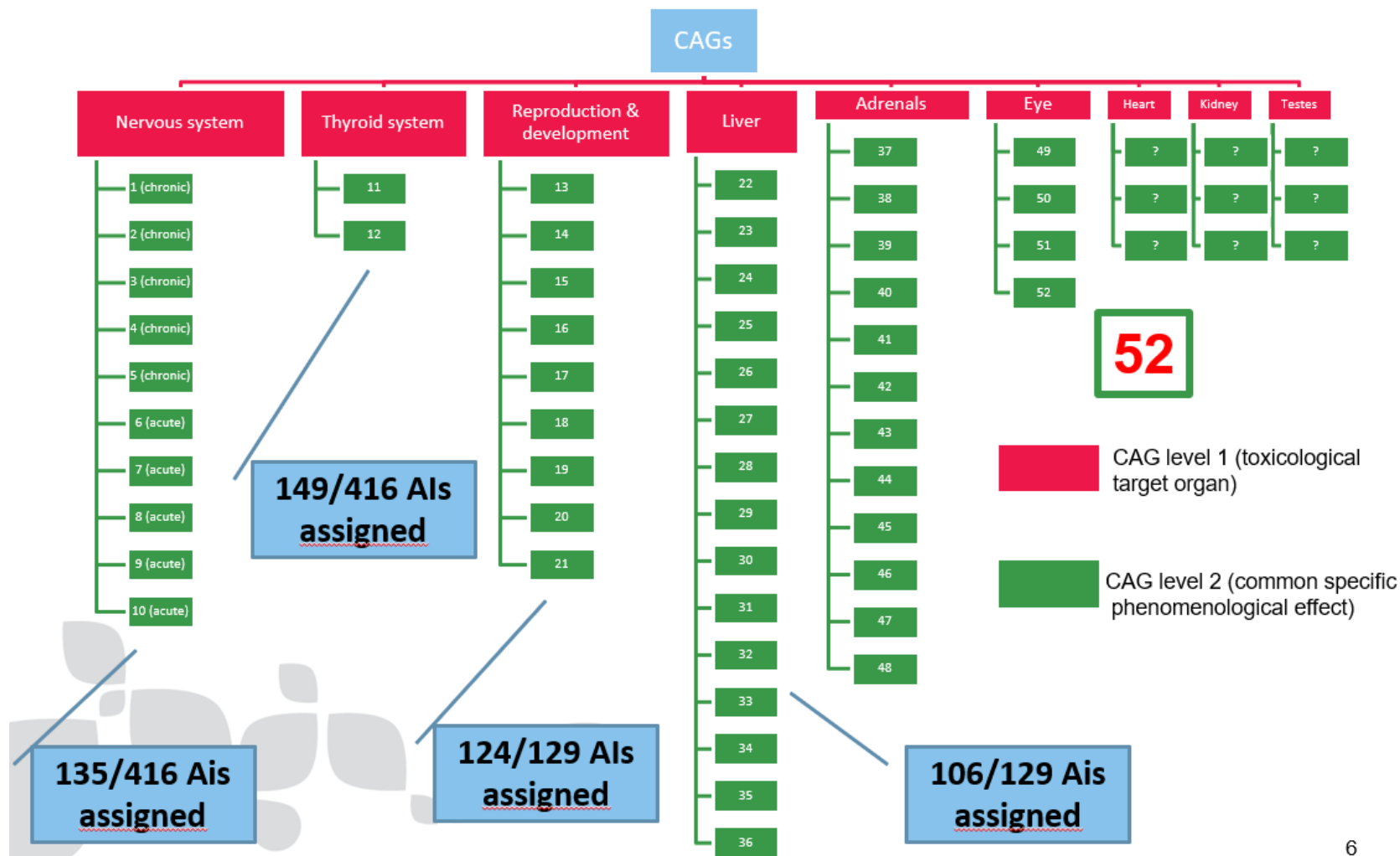
Exclusion

Only based on  
specific data

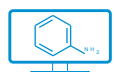
First CAGs were proposed for the  
**Thyroid (chronic)**  
**Nervous system (chronic and acute)**

CAG – Cumulative Assessment Groups

# Cumulative Assessment Groups - Slide shown in 2017



6

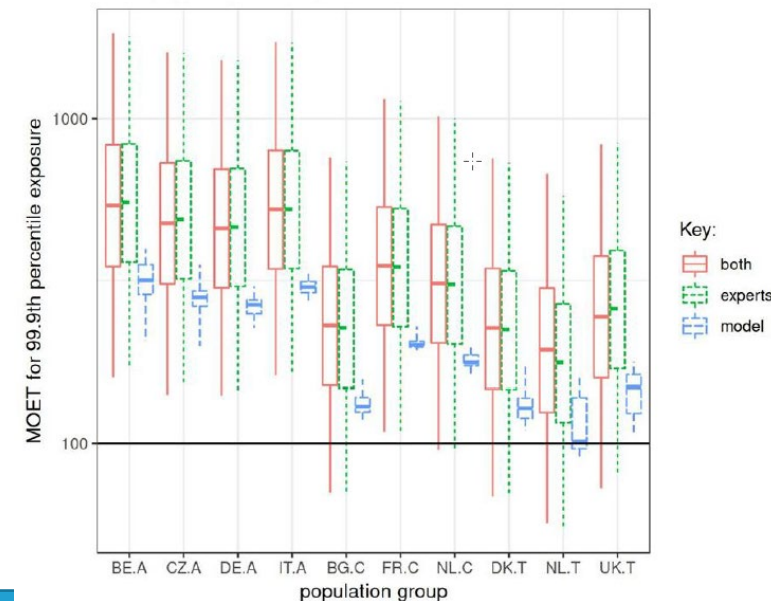


**Toxicology**  
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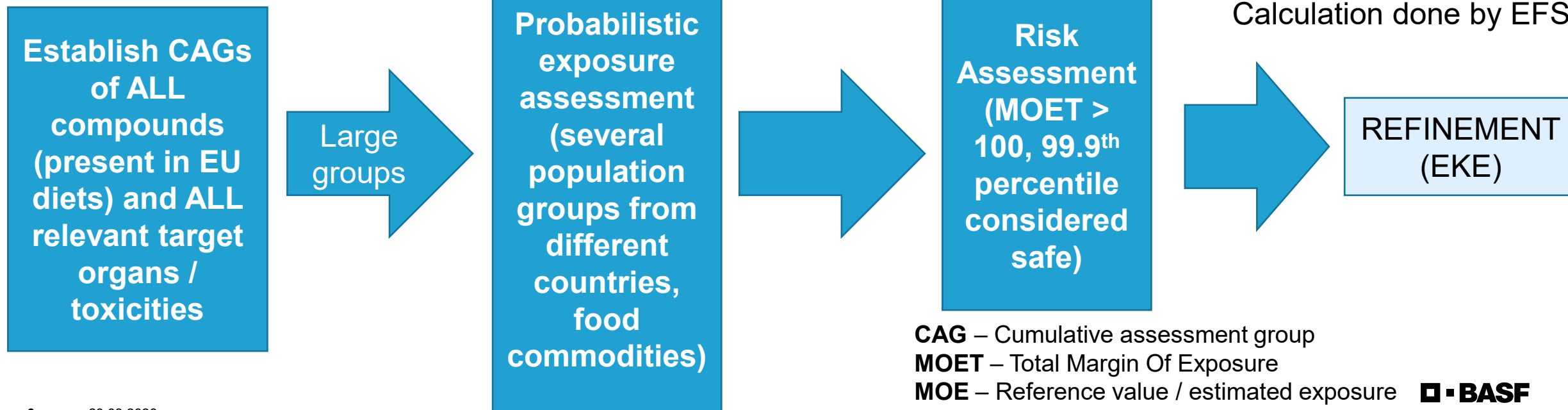
# European Approach – Principles of Cumulative Dietary Risk assessment of pesticide residues

Overall assumption: Dose additivity in case of common toxicity

## Hypothyroidism



Calculation done by EFSA



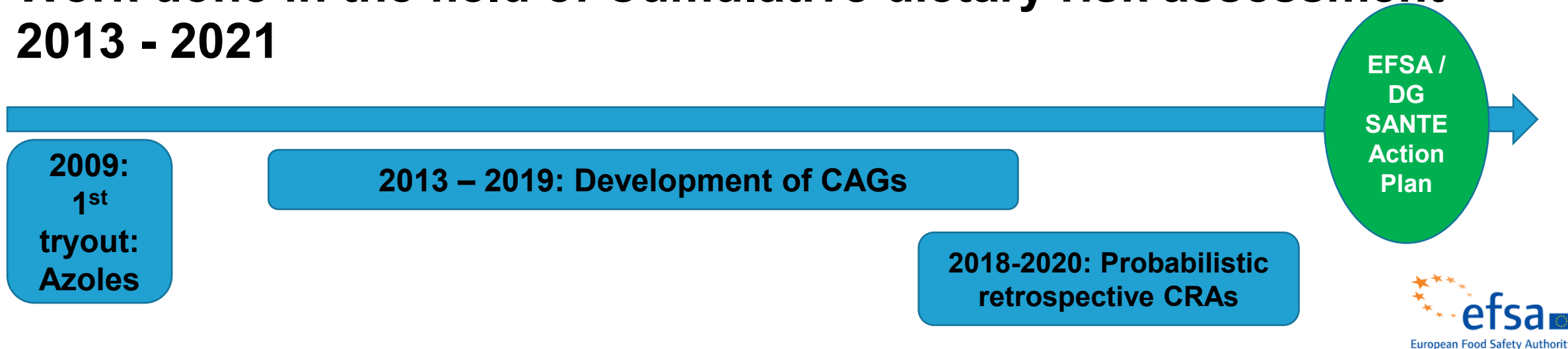
**CAG** – Cumulative assessment group

**MOET** – Total Margin Of Exposure

**MOE** – Reference value / estimated exposure

**EKE** – Expert Knowledge Elicitation

# Work done in the field of Cumulative dietary risk assessment – 2013 - 2021

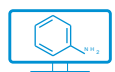


## Cumulative Assessment Groups (CAGs)

- 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



7

23.03.2026

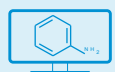


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# Cumulative Assessment Group – example chronic thyroid group

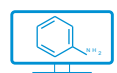
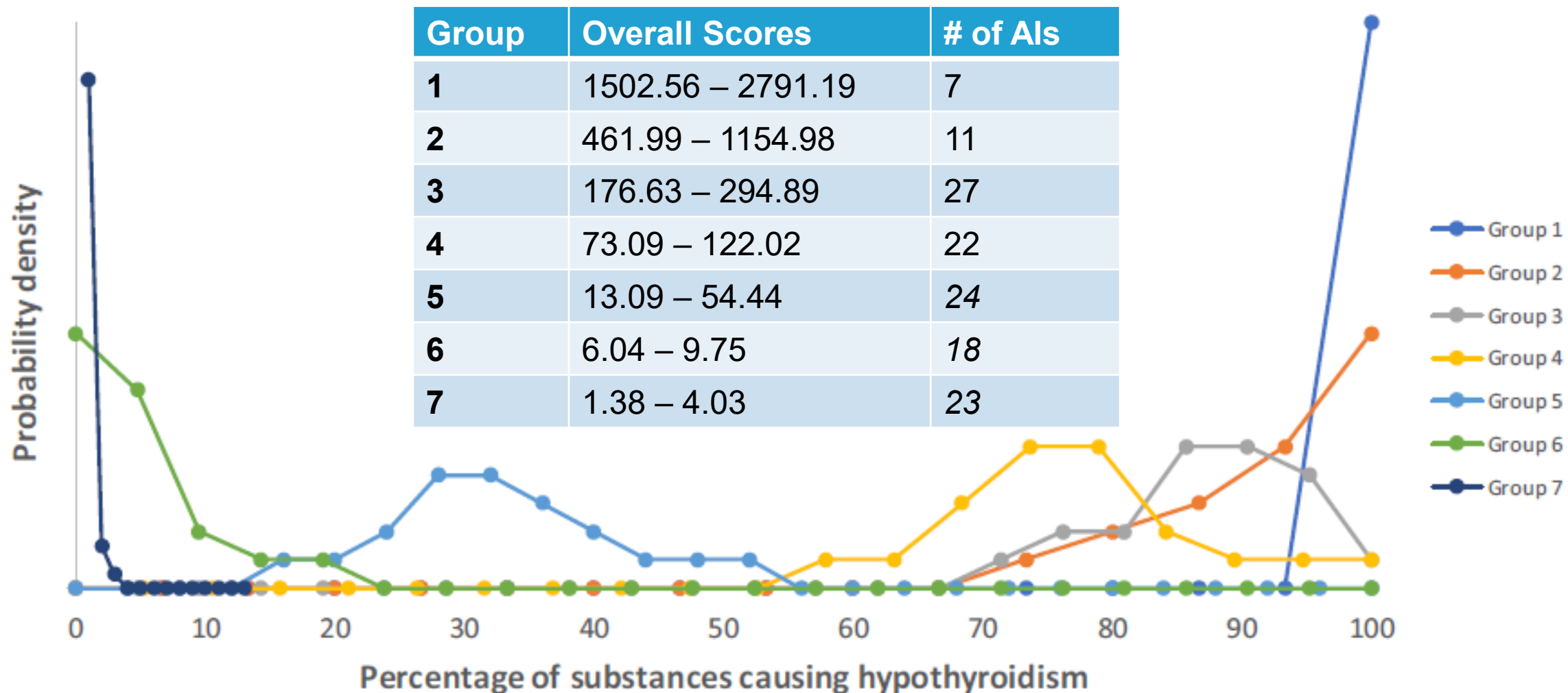
Substances included in the CAG for hypothyroidism										
Active substance	Lines of evidence									New S
	Decrease in serum T4 and /or T3 levels Yes=++, No=0, /=not measured	Increase in serum TSH levels Yes=++, No=0, /=not measured	Follicular cell hypertrophy/hyperplasia Yes=++, No=0	Increase relative thyroid weight Yes=++, No=0	Follicular cell tumours Yes=++, No=0	Is the effect showing a progressive nature? Yes=+++, No=0	Are all the effects observed dose related? Yes=+++, Yes at high dose=+, No=0	Is the effect observed in a second species? Yes=+ or Not=0	Is the effect supported by a mechanism of action? 0=No, +=presumed, ++=Yes	
	<b>2,17</b>	<b>2,50</b>	<b>2,42</b>	<b>1,38</b>	<b>2,42</b>	<b>2,92</b>	<b>5,58</b>	<b>2,92</b>	<b>3,92</b>	
Substance A	++	/	++ (higher NOAEL)	++ (higher NOAEL)	++	+++	+++	0	++	2791,19
Substance B	++	++	++	++	++ (higher NOAEL)	+++	+++	+ (mouse)	+	2078,55
Substance C	/	/	++	++	++	+++	+++	+ (dog)	+	2078,55

**Overall scores**



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# Cumulative Assessment Group – example chronic thyroid group

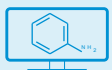


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# Relevant outcomes and learnings from the first retrospective cumulative dietary risk assessments

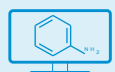
- In all cases, „cumulative exposure does not reach the thresholds for regulatory consideration for all the population groups considered.“
- In the worst-case scenarios, the impact of uncertainties has been identified and exposures and hazards have been refined (Expert Knowledge Elicitation (EKE) process).
- 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 due to lacking data (e.g. processing factors, use frequencies)
- Hazard refinements possible by deriving Benchmark Doses (BMDs)



# EFSA / DG SANTE Action Plan



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

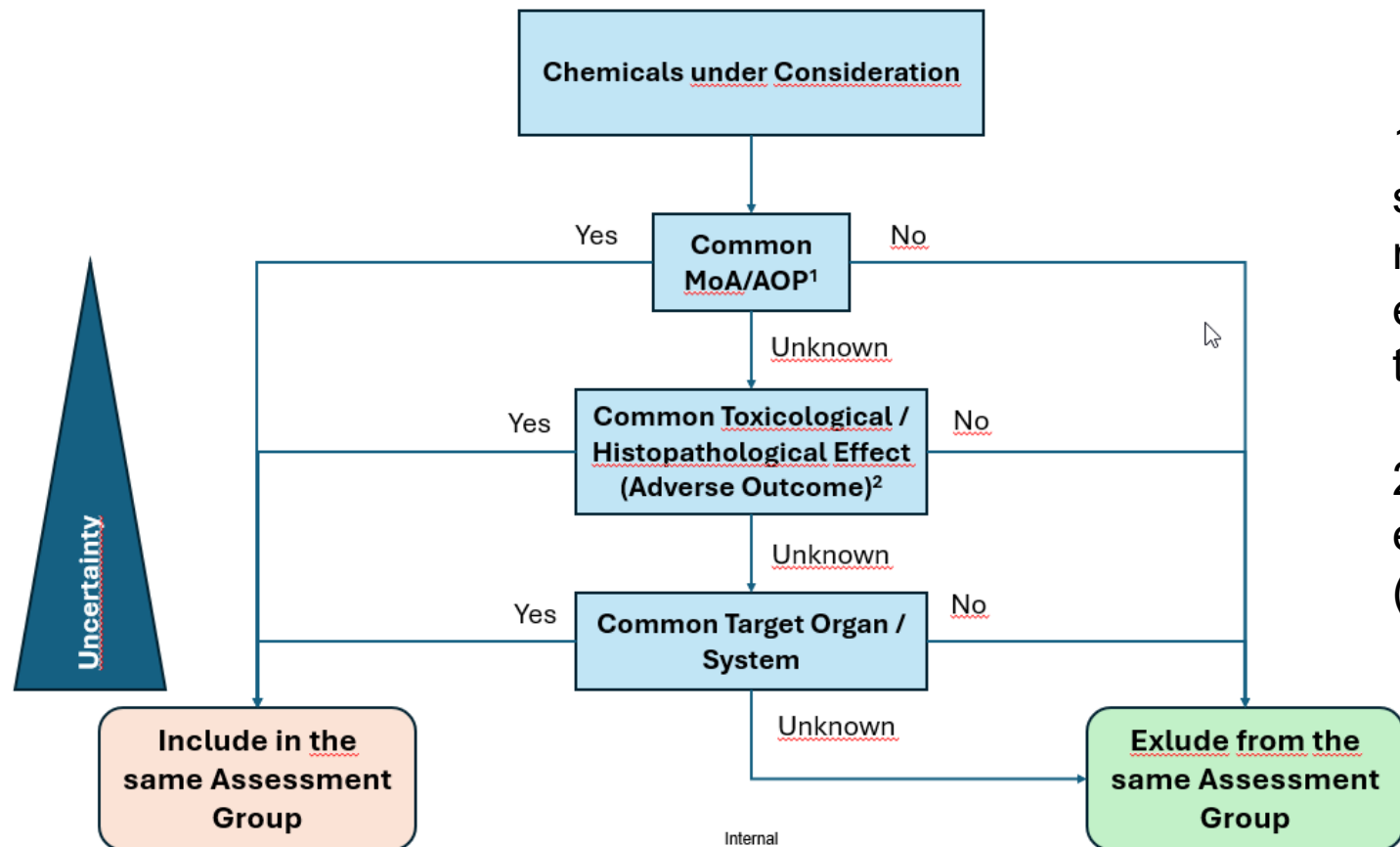


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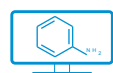


# Critical appraisal of the EKE to identify uncertainties in hazard-based grouping



1 – Evidence for similar mechanisms / same key events, e.g. craniofacial malformation AOPs (check e.g. relevant key events e.g. Cyp26 + IVIVE, or triglyceride accumulation + IVIVE)

2 – see examples for liver grouping (Foster et al., 2020), suggested kidney grouping (EFSA SO, kidney)

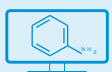


# EKE appraisal for the CAG on craniofacial malformations

- Identification of lines of evidence to determine uncertainties in likelihood of (truly) belonging to the group

1	At least one indicator has been observed in toxicological studies
2	The substance belongs to a chemical class (known for dev tox effects)
3a	Dose-relationship
3b	Indicators of the specific effect at the highest dose only.
3c	Effect in at least two dose levels without dose-response relationship
3d	The specific effect at no dose related incidence
3e	the specific effect at the only dose tested
4	Absence of maternal toxicity
5	At least one of the indicators has been observed in more than one study in the same species.
6	Indicators of the specific effect have been observed across species.

<https://doi.org/10.1016/j.reprotox.2024.108753>



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- Identification of specific indicators for grouping into CAG-DAC (abnormal skeletal development) and CAG-DAH (head soft tissue alterations and brain neural tube defects)

## CAG – DAC specific indicators

Facial fissure	facial cleft (prosoposchisis, gnatoschisis) cleft palate (palatoschisis, uranoschisis) cleft lip (cheiloschisis, harelip) cheilognathoschisis (syndromic, including cheilognathopalatoschisis (syndromic, inc (not really a fissure, but a parameter of a
Jaw/Nasopharynx	any kind of shortening/enlarging/fusion o
Eye	open eye/open eyelid/ablepharia
Ear	any kind of abnormality described at skel
Hyoid <sup>a</sup>	any kind of hyoid defects (bent or accent ossification in the context of a general de
Skull vault	exencephaly/cranioschisis/acrania (note:
agenesis	(brain not formed), when only secondaril
Skull defects <sup>a</sup>	includes any abnormality (agenesis/absen squamosal, supraoccipital) with the excep
Tongue	Extra ossification sites/accessory skull bo tongue protrusion (indicator of shortenin
Others	Abnormalities at the branchial apparatus

# Results from the evaluation of CAG-DAC membership probability assessment

Substance	LOE 1 ≥ 1 indicator observed	LOE 2 Chemical class	LOE 3 Dose-response scenarios	LOE 4 Absence of maternal tox	LOE 5 Indicator in >1 study	LOE 6 Across species	Additional elements	Probability Range
2,4-D	Yes	No	Indicators only seen at high dose	No	No (rats) n.a. (rabbits)	Yes	+ supporting probability - lowering probability + unambiguousness of observed indicator in rabbit (cleft palate) - only one fetus was affected in rabbits; indicators in rats (exencephaly, agnathia) were observed in the fetus and were not repeated	33 – 90%
Chlorpyrifos	Yes	No	Indicators only seen at high dose	No	No (rats) n.a. (rabbits)	No	+ unambiguousness of the observed indicator (cleft palate) - only one fetus affected and studies available in 3 species (rats, rabbits, mouse)	10 – 50%
Folpet	Yes	No	Incidences not dose-related	Yes	No (rats) No (rabbits)	Yes	+ uncertainty in assignment of dose-response in rabbits as no. of affected fetuses is low; dose-response observed in rats - indicator observed in rats (anterior fontanelle large) is not very specific, and was found in high incidence in controls	40 – 70%
Mancozeb	Yes	Yes	Dose-response	Yes	Yes (rats) No (rabbits)	No	+ mammalian rat metabolite (ETU) causes similar effects; unambiguousness of effect (cleft palate)	75 – 90%
Tebuconazole	Yes	Yes	Dose-response	Yes	Yes (rats) Yes (rabbits)	Yes	+ observation in 3 species (rats, rabbit, mouse), observation of effect after dermal exposure - one rabbit study (dosed equivalently to the rat study) did not show the effect; dose response seen in mice, but not in other species	90 – 99%
Thiabendazole	Yes	Yes	Dose-response	No	N.A. (rats) No (rabbits)	No	- only one indicator observed (enlarged anterior and posterior fontanelles) studies available in 3 species (rats, rabbits, mouse) but effects only observed in rabbits (although only 1 rats/mice study was clearly dosed high enough)	33 – 90%

Large probability ranges are not useful for decision taking

ECHA RAC decision should be taken into consideration

Compounds with low probability ranges could be removed from the CAG

Usefulness of the EKE methodology can be questioned

# EFSA Prioritization



- 2-step prioritization analysis
- Monitoring cycle 2019 – 2021
  - ▶ Consumption of 36 raw primary commodities
  - ▶ Total of 371 substances → 350 were used for analysis
- Conduct probabilistic exposure calculations for acute and chronic exposure (on selected occurrence and consumption data)

## How Europe monitors pesticide residues in food

**133,000**  
SAMPLES  
COLLECTED IN 2023

Crops that have been treated with pesticides may contain residues. To ensure that pesticides are used correctly and their residues do not pose a risk to consumers, legal limits are set in EU legislation.

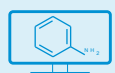
How do we know that levels of residues found in food are safe?

Food inspection services in the EU, Iceland and Norway have monitoring programmes in place to check that food complies with legal limits.

100%  
75%  
50%  
25%  
0%

**98%**

of samples in 2023 were free of residues or contained residues that were within legal limits



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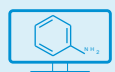
# EFSA Prioritization for substances

- Hazard quotients (HQ) have been assessed for each of the 350 substances

$$\text{HQ} = \frac{\text{Exposure of the individual substance}}{\text{Individual HBGV}}$$

- HQ below 0.1 at the 99.9th percentile were considered having a marginal contribution to cumulative exposure
- Final priority list of substances is composed by **67 substances** (out of 350) fulfill the criteria of **HQ ≥ 0.1**

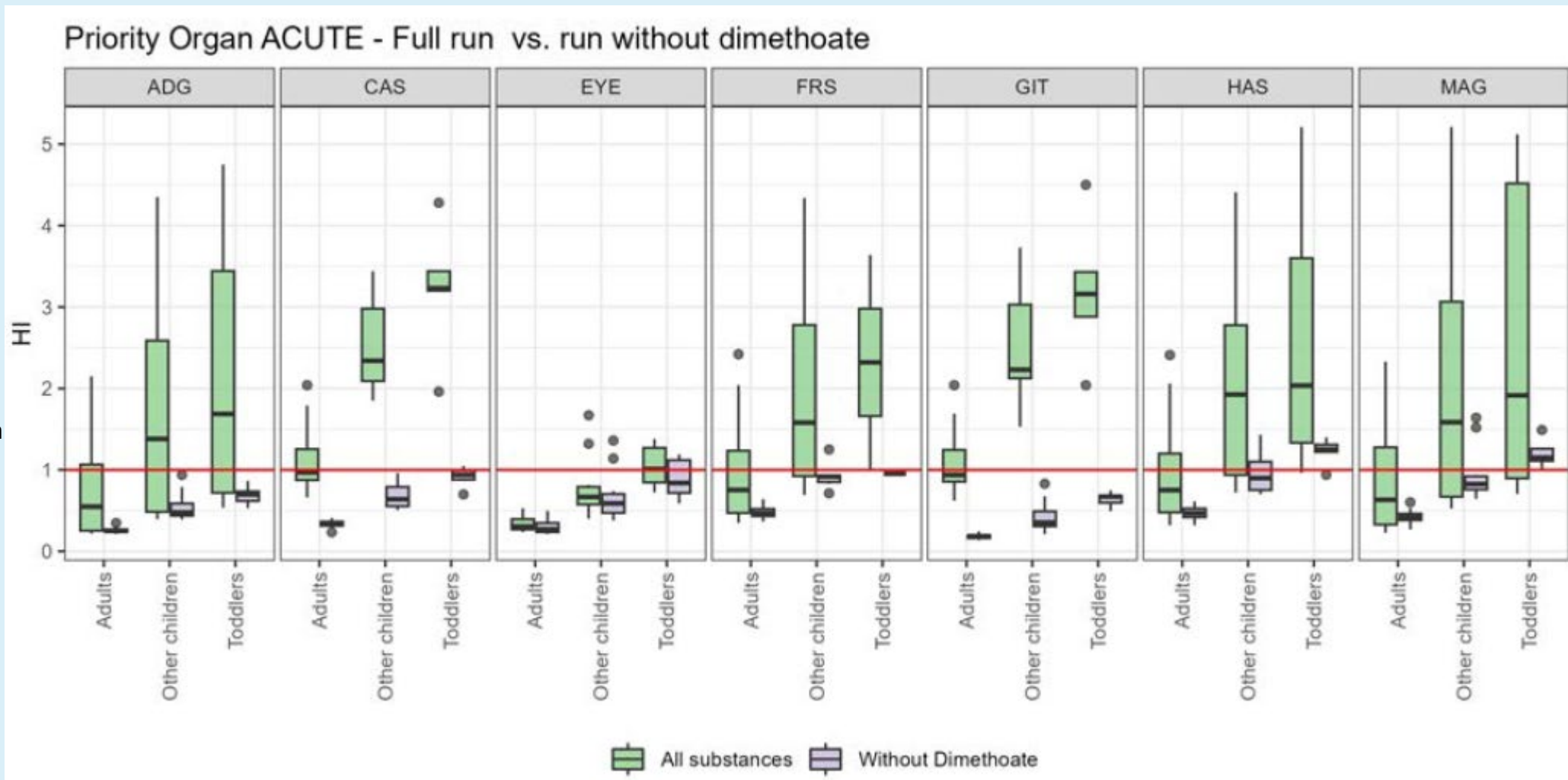
HBGV = Health based guidance value, e.g. ADI



# Hazard Index (HI) calculations for specific organ systems

HI =  $\sum$  HQs  
Organ-specific

Organs with  
HI  $\geq 1$  (at the 99.9<sup>th</sup>  
percentile)



# EFSA Prioritization for Cumulative Assessment Groups (CAGs)

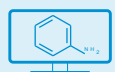
## Chronic

Range of median HI values by population class and N survey above HI = 1

Organ system	Adults	N surveys	Other children	N surveys	Toddlers	N surveys
ADG	0.15–0.33	[0/15]	0.23–0.41	[0/10]	0.32–0.53	[0/5]
BOS	0.01–0.03	[0/15]	0.02–0.04	[0/10]	0.03–0.06	[0/5]
CAS	0.2–0.46	[0/15]	0.37–0.68	[0/10]	0.46–0.72	[0/5]
EYE	0.09–0.21	[0/15]	0.18–0.31	[0/10]	0.22–0.43	[0/5]
FRS	0.26–0.73	[0/14]	0.41–0.67	[0/6]	0.69	[0/1]
GIT	0.14–0.36	[0/15]	0.22–0.44	[0/10]	0.3–0.59	[0/5]
HAS	0.26–0.59	[0/15]	0.44–0.85	[0/10]	0.57–0.94	[0/5]
KID	0.22–0.49	[0/15]	0.33–0.73	[0/10]	0.43–1.07	[1/5]
LIV	0.31–1.41	[1/15]	0.52–1.24	[3/10]	0.96–1.72	[4/5]
MAG	0.25–0.54	[0/15]	0.43–0.87	[0/10]	0.57–0.94	[0/5]
MRS	0.3–0.73	[0/14]	0.55–1.26	[2/6]	1.16	[1/1]
MUS	0.19–0.42	[0/15]	0.33–0.76	[0/10]	0.5–0.78	[0/5]
PAG	0.01–0.06	[0/15]	0.02–0.12	[0/10]	0.04–0.09	[0/5]
PIG	0.09–0.21	[0/15]	0.13–0.3	[0/10]	0.23–0.43	[0/5]
RDT	0.34–1.41	[1/15]	0.59–1.3	[3/10]	1.03–1.85	[5/5]
URB	0.17–0.35	[0/15]	0.29–0.59	[0/10]	0.41–0.62	[0/5]

**Organ system:** ADG: adrenal gland; BOS: bones/skeleton; CAS: cardiovascular system; EYE: eye; FRS: female reproductive system; GIT: gastrointestinal system; HAS: haematopoietic system and haematology; KID: kidney; LIV: liver; MAG: mammary gland; MRS: male reproductive system; MUS: muscular system; PAG: parathyroid gland; RDT: reproductive and developmental toxicity; URB: urinary bladder.

- **Prioritized CAGs:**
  - ▶ KID
  - ▶ LIV
  - ▶ MRS
  - ▶ RDT
  - ▶ HAS (from acute scenarios)
- 5 out of 16



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# Since the prioritization exercise...

## Specific effects on liver relevant for performing a dietary cumulative risk assessment of pesticide residues

European Food Safety Authority (EFSA) | Anna F. Castoldi | Tamara Coja | Anna Lanzoni | Kyriaki Machera | Luc Mohimont | Monica Nepal | Camilla Recordati | Federica Crivellente

Correspondence: pesticides.mrl@efsa.europa.eu

The declarations of interest of all scientific experts active in EFSA's work are available at <https://open.efsa.europa.eu/experts>

### Abstract

According to the 'EFSA-SANTE Action Plan on Cumulative Risk Assessment for pesticides residues', EFSA initiated a retrospective cumulative risk assessment (CRA) of the effects of pesticide residues on the liver. For this CRA, EFSA identified the following liver-specific effects in accordance with the International Harmonisation of Nomenclature and Diagnostic Criteria (INHAND): (1) hypertrophy due to enzymatic induction, liver; (2) fatty change and/or phospholipidosis, hepatocellular; (3) degeneration/cell death, hepatocellular; (4) porphyria, hepatocellular, biliary duct; (5) cholestasis, hepatocellular, biliary duct; (6) preneoplastic and neoplastic changes, hepatocellular; (7) neoplastic changes, biliary duct. In addition, as gallbladder is part of the extrahepatic biliary system and can be affected by hepatic toxicity, the following specific effects in the gallbladder were defined: (1) erosion/ulceration, gallbladder (2) calculi, gallbladder and (3) neoplastic changes, gallbladder. Histopathology was considered as the most appropriate source of evidence together with the increase in relative liver weight, and a list of indicators was defined and will be used to collect information on these specific effects as included in the assessment reports of the different active substances used as plant protection products. The criteria for inclusion of active substances/metabolites into cumulative assessment groups (CAGs) were also defined, together with the hazard characterisation methodology and the lines of evidence for assessing CAG-membership probabilities. While primary indicators define the specific effect, secondary indicators and other endpoints (named ancillary endpoints) are considered not sufficiently informative to indicate a specific effect but are rather contributing to the overall evidence; these will be collected only for a limited number of substances (i.e. risk drivers based on hazard and exposure considerations) for determining the likelihood of the substances truly belonging to the CAGs (CAG-membership probabilities). Considering that it is not considered appropriate to establish CAGs for acute liver effects, CRAs on the liver will be only focused on chronic exposure. The process of data extraction and actual establishment of the CAGs is beyond the scope of this report. This part of the CRA process was outsourced and will be the subject of a separate report.

### KEYWORDS

cumulative assessment groups, cumulative risk assessment, gallbladder, liver, pesticide residues, specific effects

External Scientific Report



APPROVED: XX Month 20XX  
doi: 10.2903/sp.efsa.20YY.EN-NNNN

## Data collection, hazard characterisation and establishment of cumulative assessment groups in view of the cumulative risk assessment of pesticides for reproductive function including fertility

Tamara Coja, Lena Brunner, Sonia Galazka, Daniela Hofstädter, Melanie Kuffner, Ulrike Mayerhofer, Elke Rauscher-Gabernig, Hao Sun

Austrian Agency for Health and Food Safety, Division Integrative Risk Assessment, Data and Statistics (DSR), Austria

### Abstract

The aim of the present report is to collect data on indicators of specific effects on reproductive function, including fertility from various pesticides and their metabolites and, subsequently, to establish cumulative assessment groups (CAGs), in view of performing cumulative risk assessment (CRA) of pesticide residues for effects on reproductive function, including fertility. For this purpose, a list of previously defined indicators of the specific effects was consulted to retrieve the relevant data from assessment reports. Toxicological data from 46 prioritised pesticide active substances and five identified metabolites were collected from regulatory documents. For each substance a LOAEL was derived for the most sensitive indicator(s) of the specific effect. All six originally defined specific effects and the respective CAGs were populated: 1) altered male mating performance; 2) altered female mating performance; 3) decreased male fertility; 4) decreased female fertility; 5) altered gestation; 6) altered parturition. The identified uncertainties in the allocation of the substances in the different CAGs were highlighted. Overall, this project utilises the methodology previously developed and described in the EFSA report dealing with the identification of specific effects on reproductive function, including fertility and it provides a comprehensive hazard characterisation of substances.

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**Keywords:** reproductive function, fertility, cumulative risk assessment, cumulative assessment groups, pesticides

External scientific report



APPROVED: 09 February 2026  
doi: 10.2903/sp.efsa.2026.EN-9965

## Data collection, hazard characterisation and establishment of cumulative assessment groups in view of the cumulative risk assessment of pesticide residues for kidneys

Kyriaki Machera<sup>1</sup>, Anastasia Spyropoulou<sup>1</sup>, Eliana Spilioti<sup>1</sup>, Dimitra Nikolopoulou<sup>1</sup>, Niki Arapaki<sup>1</sup>

<sup>1</sup> Benaki Phytopathological Institute, Scientific Directorate of Pesticides' Control & Phytopharmacy, Laboratory of Pesticides' Toxicology

### Abstract

The aim of the present report is to collect data on the toxic effects of various pesticides and their metabolites on the kidneys and subsequently establish cumulative assessment groups (CAGs) to facilitate cumulative risk assessment (CRA) of pesticide residues affecting kidney health. For this purpose, a list of previously defined specific effects and the respective indicators was used to retrieve and organise the relevant data. The specific effects and the respective CAGs considered were glomerular injury, tubular injury, tubular crystals, papillary necrosis, interstitial nephritis, pelvis erosion/ulceration, pelvis calculi/crystals, renal preneoplastic and neoplastic lesions and pelvis preneoplastic and neoplastic lesions. Toxicological data from 35 prioritised pesticide active substances and 3 metabolites were collected from regulatory documents. For each substance a NOAEL and a LOAEL were derived based on the most sensitive histological indicator of the specific effect. Substances were assigned into 9 CAGs for chronic effects and 4 CAGs for effects of acute nature, based on the indicators observed. The identified uncertainties in the CAG allocation and characterisation of the substances were highlighted. Overall, this project utilises the methodology previously developed and described in the EFSA report dealing with the identification of specific effects on kidneys and it provides a comprehensive hazard characterisation of substances affecting the different renal topographical regions.

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**Keywords:** kidney, pesticides, histopathology, cumulative assessment group, cumulative risk assessment

# Comments on the Reproduction / Dev tox CAG / CRA

- Only very few substances have LOAELs below 10 mg/kg bw
- Table does not reflect the individual margin of exposure between overall LOAEL and effect-specific LOAEL
- It could be considered to remove substances which show reproduction effects at doses >10 above the overall LOAEL (used for reference level derivation)

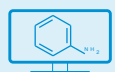
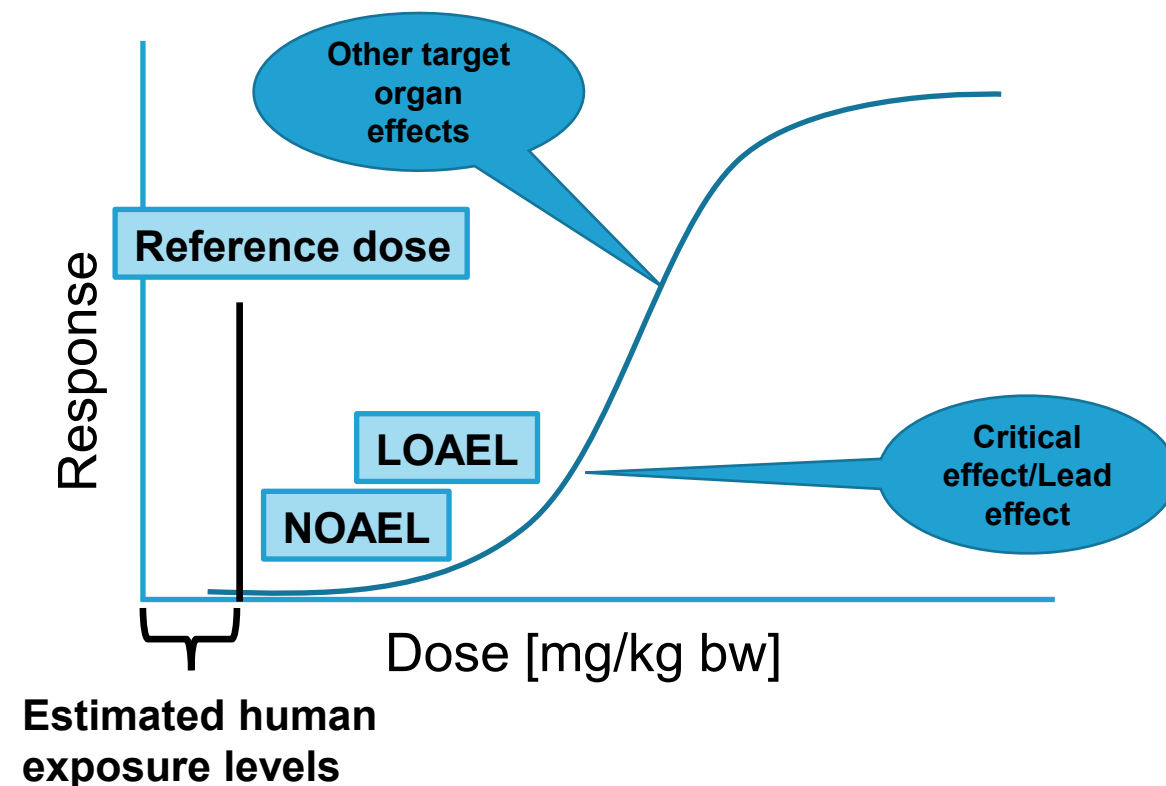
Substance	Decreased female fertility	Decreased male fertility	Altered gestation	Altered male mating performance	Altered female mating performance	Altered parturition	Total CAGs
dimethoate	0.08	0.08	9.5	9.5	9.5		5
omethoate	2.26	1.2	2.26	1.2	2.26		5
fipronil	28.4	26		26	28.4		4
tetraconazole	34.2	25.9	0.8			0.8	4
imazalil	80	80	80			80	4
dimethylformamide (DMF)	820	820		1455	1455		4
dicofol p,p'	2		10	2			3
hexachlorobenzene (HCB)	14.4	14.4	28.8				3
dieldrin	0.0155	0.0155					2
heptachlor	0.65	0.65					2
hexachlorocyclohexane (HCH) beta isomer	0.9	0.9					2
emamectin	1.8	3.6					2
oxamyl	6.1	4.9					2
propineb	10	10					2
hexachlorocyclohexane (HCH) gamma isomer, lindane	16.6	17.6					2
propylene thiourea (PTU)	20.2	17.9					2
ethoprophos	31.6	31.6					2
cypermethrin	50	50					2
methiocarb	76.5	52.4					2
oxyfluorfen	106	91					2
1,2,4-triazole	218	15.4					2
chlormequat chloride	277	241					2
pyrimethanil	466	477					2
tau-fluvalinate	91						1
ethylene urea (EU)		76					1
abamectin*							0
chlorates*							0
chlordane*							0
chlorpropham*							0
chlorpyrifos*							0
cyhalothrin-gamma*							0
cyhalothrin-lambda*							0
cypermethrin-alpha*							0
cypermethrin-beta*							0
fenamiphos*							0
fenpropimorph*							0
fluometuron**							0
fluquinconazole*							0
haloxyfop-p*							0
maleic hydrazide*							0
mancozeb*							0
maneb*							0
methomyl*							0
metiram*							0
nicotine*							0
phosphonic acid*							0
pirimiphos-methyl*							0
prosofocarb*							0
thiabendazole**							0
thiram*							0
ziram**							0
<b>Total substances</b>	<b>24</b>	<b>23</b>	<b>6</b>	<b>5</b>	<b>4</b>	<b>2</b>	

Indicator LOAEL mg/kg bw/d	
0.01-0.1	Red
0.1-1	Orange
1-10	Yellow
10-100	Light Green
100-1000	Green
1000-2000	Light Blue
no indicator	White

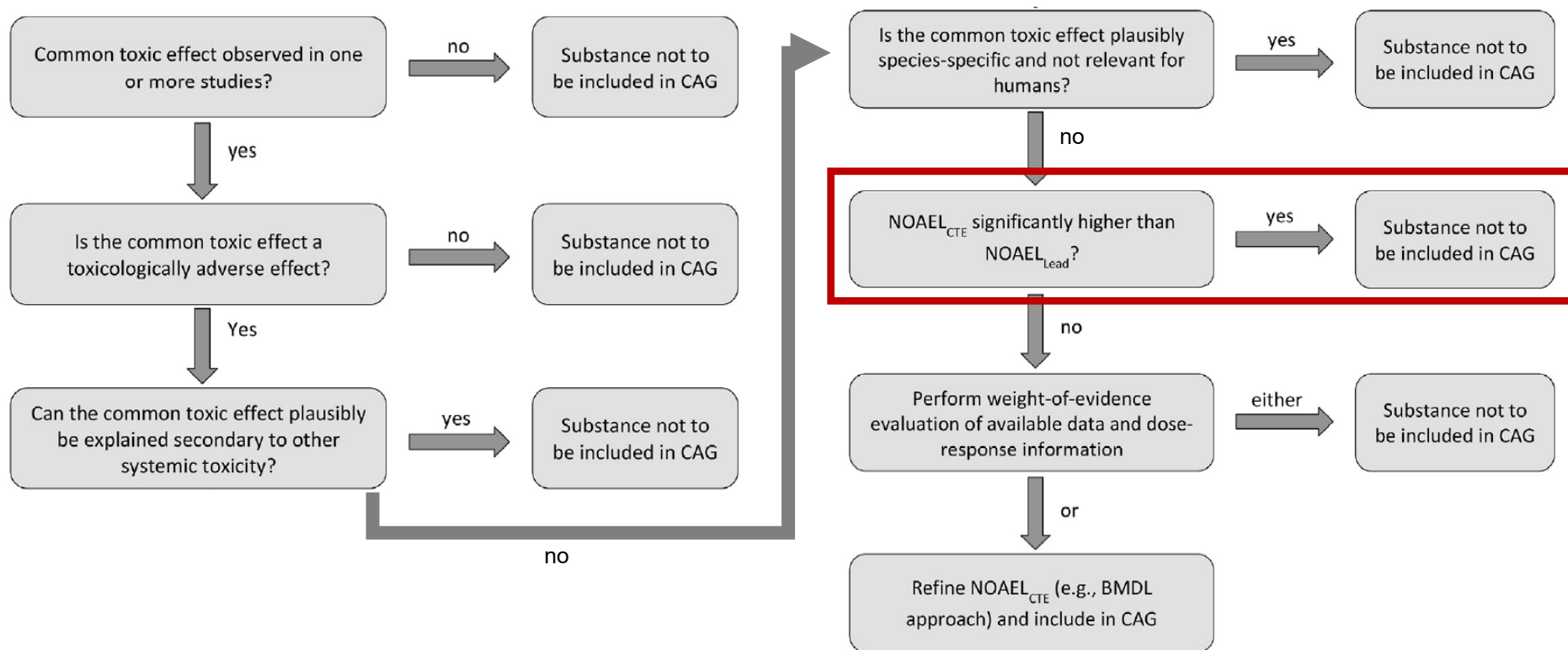
\* Substance not collected since no indicator could be identified  
 \*\* Substance not included in any CAG due to MTD exceedance/ excessive toxicity

# Apply lead effect

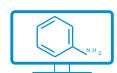
- Using the lead effect concept would reduce numbers of substances in a Cumulative Assessment Group
- Factors of e.g. 10 could be considered
- Makes the probabilistic exposure assessment more transparent and less complex



# Proposed flow scheme for more stringent criteria application



NOAEL<sub>CTE</sub> – lowest NOAEL for the Common Toxic Effect  
 \*\*NOAEL<sub>Lead</sub> – NOAEL used for ADI, ARfD



# Unsolved issues and areas for further work

- Aggregate cumulative exposures / risk assessment
  - ▶ Cumulative exposure via different routes of exposure (e.g. dietary and non-dietary pesticide)
- Prospective cumulative risk assessments
  - ▶ Relevant for MRL applications
- Combination of data / assessments across regulatory areas – identify relevant exposure scenarios
- Smart combination with biomonitoring data (PARC – Real-life-mixtures; prioritized mixtures)
- Exposome ([Home - The European Human Exposome Network \(EHEN\)](#))
- Do we need more exposure data?
- How to do Risk Management in case of exceedance of risks?

