

22 October 2019



Technical stakeholder event on cumulative risk assessment of pesticides in food

Cumulative assessment groups

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Trusted science for safe food



Methodology

Specific effects

Assessment groups

Uncertainties

SCIENTIFIC REPORT

ADOPTED: 26 June 2019

doi: 10.2903/j.efsa.2019.5801

Establishment of cumulative assessment groups of pesticides for their effects on the thyroid

European Food Safety Authority (EFSA),
Federica Crivellente, Andy Hart, Antonio F. Hernandez-Jerez, Susanne Hougaard Bennekou,
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Establishment of cumulative assessment groups of pesticides for their effects on the nervous system

European Food Safety Authority (EFSA),
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Steps before publication

- Endorsement of a first draft by the EFSA PPR Panel
- Public consultation
- Endorsement by the EFSA PPR Panel

- The methodology uses cumulative assessment groups which are populated by pesticides causing the same phenomenological effect
- The cumulative risk of pesticides from the same CAG were assumed to act together through dose-addition
- Interactions are not included in the 2013 methodology and not expected considering the low level of exposure
- Potential uncertainties regarding the applicability of the dose addition model were taken into account as part of the uncertainty analysis (reports on CRA)

422 active substances have been reviewed on the basis of:

- EU Draft Assessment Reports
- EU Renewal Assessment Reports
- Joint Meeting on Pesticide Residues evaluation reports
- US-EPA assessment reports
- Open literature – Mode of Action

- Identification of specific effects
- Characterisation of the specific effects
- Establishment of the CAGs
- Analysis of uncertainties



Methodology

Specific effects

Assessment groups

Uncertainties

Criteria

- Systemic effects, adversity, human relevance, unambiguousness

Specific effects on the **nervous system**

- Functional alterations of the motor division
- Functional alteration of the sensory division
- Functional alteration of the autonomic division
- Histological neuropathological effects
- Brain/erythrocyte acetylcholinesterase inhibition

Specific effects on the **thyroid**

- Hypothyroidism
- Effects on C-cells

Definition of the descriptors (indicators) observed in toxicological studies suggesting that an AS causes the specific effect

Functional alteration of the motor division

- Reduced motor activity
hypoactivity, recumbency (if not observed in isolation), etc.
- Increased motor activity
tremor, hyperactivity, convulsions, etc.
- Alteration of muscle strength
reduced grip strength, increased or decreased muscle tone, muscle fasciculation, weakness, inability to stand, paresis, paralysis, etc.
- Coordination
ataxia, abnormal gait, landing foot splay, etc.

Effect can be triggered by **acute** and **chronic** exposure

Definition of the descriptors (indicators) observed in toxicological studies suggesting that an AS causes the specific effect

Hypothyroidism

- Decreased circulating T3 level, decreased circulating T4 level
- Increased circulating TSH level
- Increased relative thyroid weight
- Follicular cell hypertrophy
- Follicular cell hyperplasia
- Follicular cell neoplasia, follicular cell adenoma, follicular cell carcinoma
- Evidence of a mode of action (MOA) in direct relation with hypothyroidism

Effect can be triggered by **chronic** exposure



Methodology

Specific effects

Assessment groups

Uncertainties

Inclusion criteria

- AS having a known MoA directly relevant for the specific effect
- AS showing at least one of the indicators at statistically significant level in at least 1 toxicological study rated as 'acceptable'

Exclusion criteria

- Age-related observation or observation at or above the MTD
- Absence of dose-response relationship

422 active substances have been reviewed

Thyroid

2 effects of relevance



2 CAGs retained for assessment



Hypertrophy, hyperplasia and neoplasia of C-cells (*CAG-TCP, 17 substances*)

Hypothyroidism
(*CAG-TCF, 128 substances*)

8 with known MoA

Nervous system

5 effects of relevance



2 CAGs retained for assessment



Brain and/or erythrocyte AChE inhibition
(*CAG-NAN, 47 substances*)

Alterations of the motor division
(*CAG-NAM, 119 substances*)

84 with known MoA

Thyroid

- NOAELs for long-term exposure
- Most sensitive indicator
- Effects on C-cells covered
- Index compounds proposed

Nervous system

- NOAELs for short- and long-term exposure
- Most sensitive indicator
- Effects on sensory & autonomic system & neuropathological covered
- Index compounds proposed



Methodology

Specific effects

Assessment groups

Uncertainties

Uncertainty question - Right group?

How sure is it that all the ASs included in the CAG cause hypothyroidism ?

- Guidance of the EFSA SC on the use of the weight of evidence approach in scientific assessments
- Guidance of the EFSA SC on expert knowledge elicitation in food and feed safety risk assessment

How sure is it that all ASs causing hypothyroidism are included?

- Considered in the overall uncertainty analysis – The Cumulative Risk Assessments

Questions

Thyroid

Does this chemical cause hypothyroidism, defined as a dose-related increase of any size in incidence and/or severity of hypertrophy and/or hyperplasia and/or neoplasm over any dose range in thyroid follicular cells of one or more laboratory mammal species?

Nervous system

Does this chemical cause any functional alteration of the motor division of the nervous system (locomotor activity, muscular strength and coordination)?

Thyroid Hypothyroidism

Known MoA: 6.5

Dose-response relationship: 6.1

2 species: 4.8

NOAEL for hypothyroidism same level as or does not differ by a factor exceeding from the NOAEL leading to the ADI: 4

Follicular cell hyperplasia: 3.5

Follicular cell tumours: 3.5

Increased serum TSH levels (or serum TSH levels unmeasured): 2.9

Follicular cell hypertrophy: 2.6

Decreased serum T4 and/or T3 levels (or serum T4 and T3 levels unmeasured): 2.4

Increased relative thyroid weight: 1.5

Nervous system

Motor division

AS with relevant MoA: 32000

AS for which a MoA is presumed: 3

Decreased motor activity: 2-4

Increased motor activity: 3-4

Muscular strength: 3-4

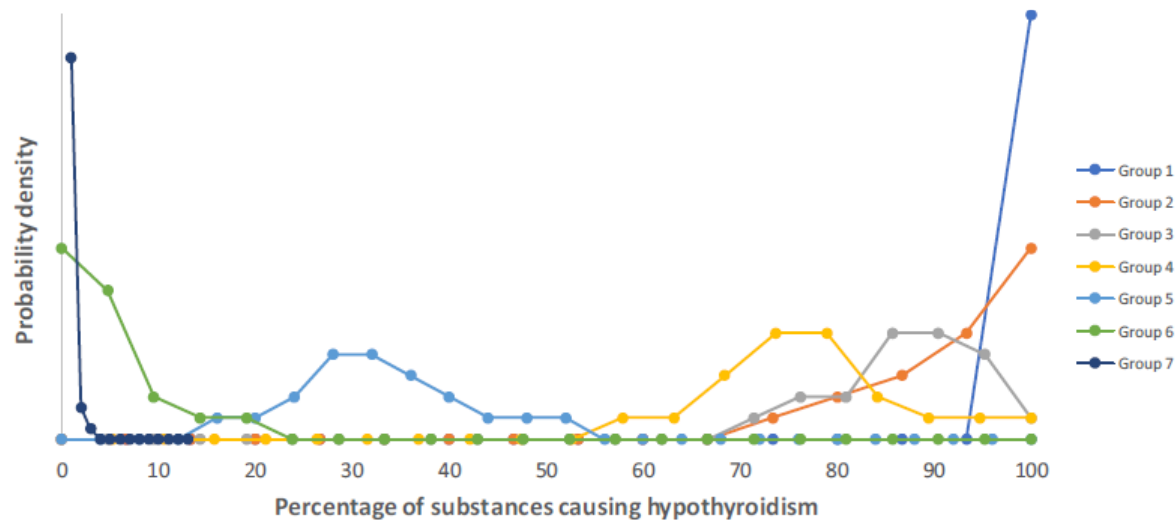
Motor coordination: 3-4

More than one species: 3

Concomitant obs. of indicators of functional alteration of the sensory function: 3-4

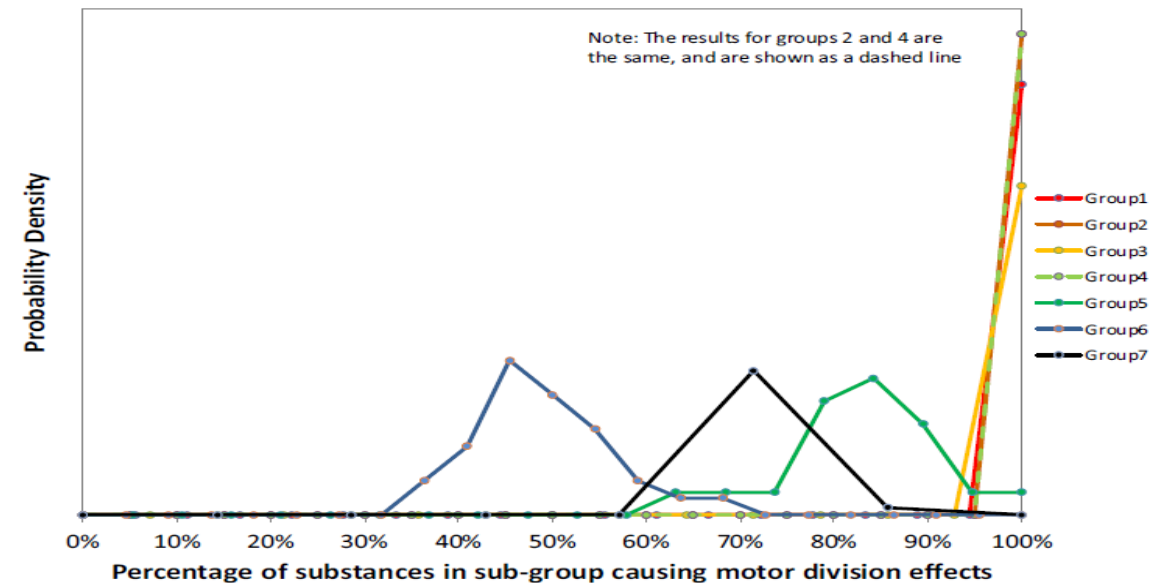
Dose-response relationship: 4

Hypothyroidism



Distributions quantifying uncertainty about the percentage of substances in each subgroup that cause hypothyroidism. The vertical axis (probability density) quantifies the experts' judgement of the likelihood of different proportions of substances causing hypothyroidism within each subgroup

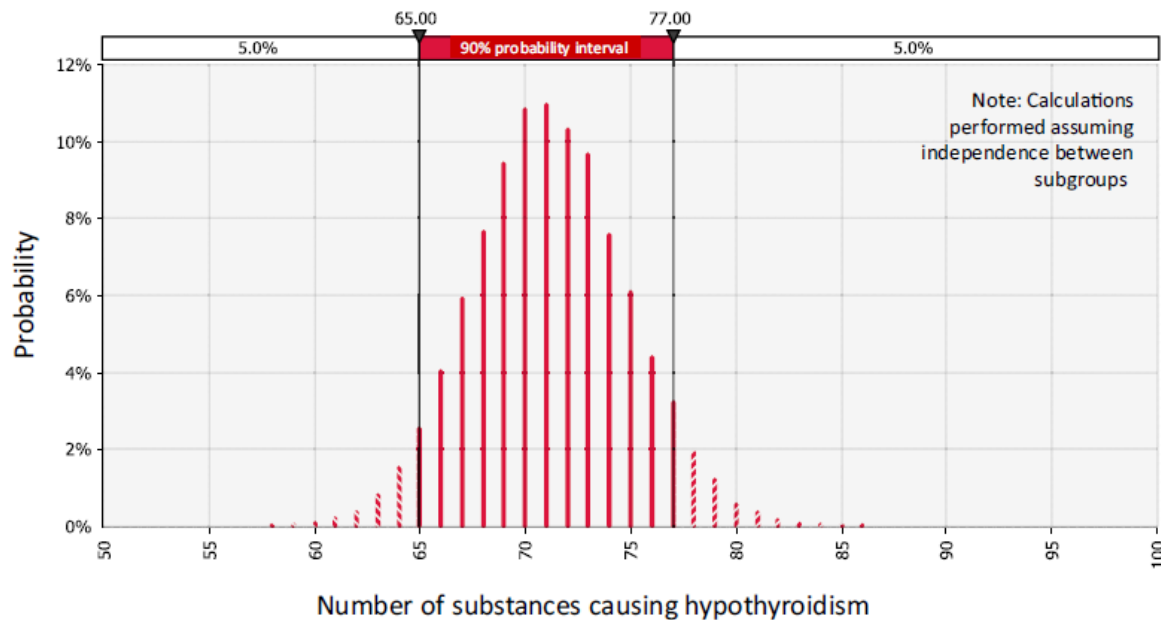
Motor Division



Distributions quantifying uncertainty about the percentage of substances in each subgroup that cause effects on the motor division. The vertical axis (probability density) quantifies the experts' judgement of the likelihood of different proportions of substances causing effects on the motor division within each subgroup

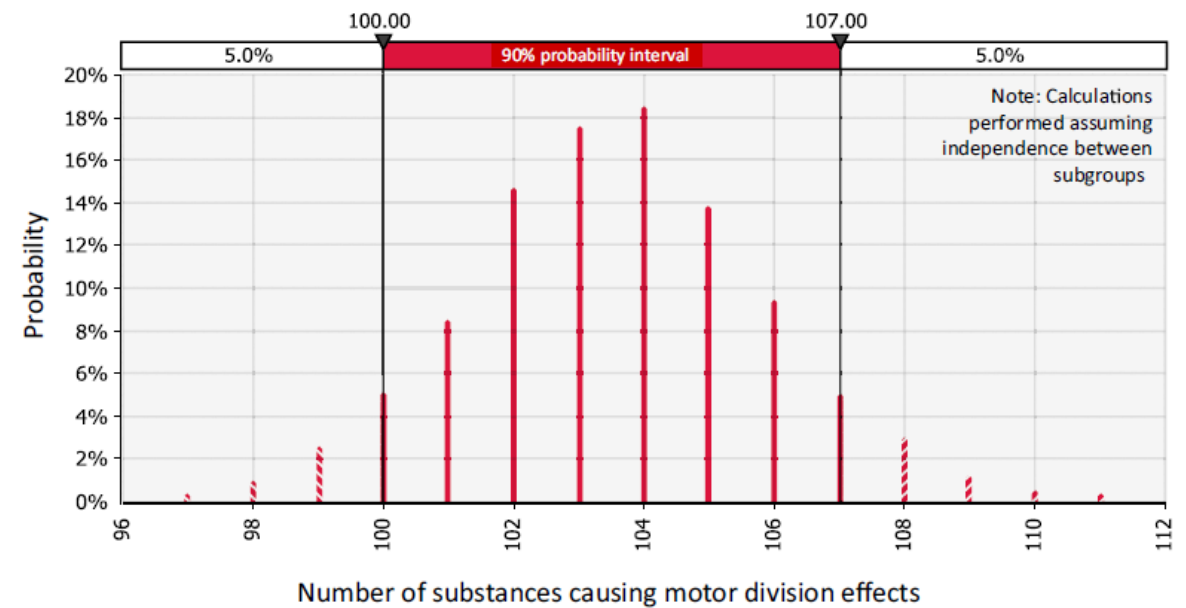
Step 6 – EKE – summarising outcome

Hypothyroidism



Distribution quantifying uncertainty about the total number of substances from subgroups 1 to 7 that cause hypothyroidism, obtained using Monte Carlo simulation assuming that the elicited distributions for the seven subgroups are independent

Motor Division



Distribution quantifying uncertainty about the total number of substances from subgroups 1 to 7 that cause effects on the motor division, obtained using Monte Carlo simulation assuming that the elicited distributions for the seven subgroups are independent

- Tested for different effects
 - **Cranio-skeletal effects**
 - Liver steatosis

Data presented at EuroMix workshop
March 2019

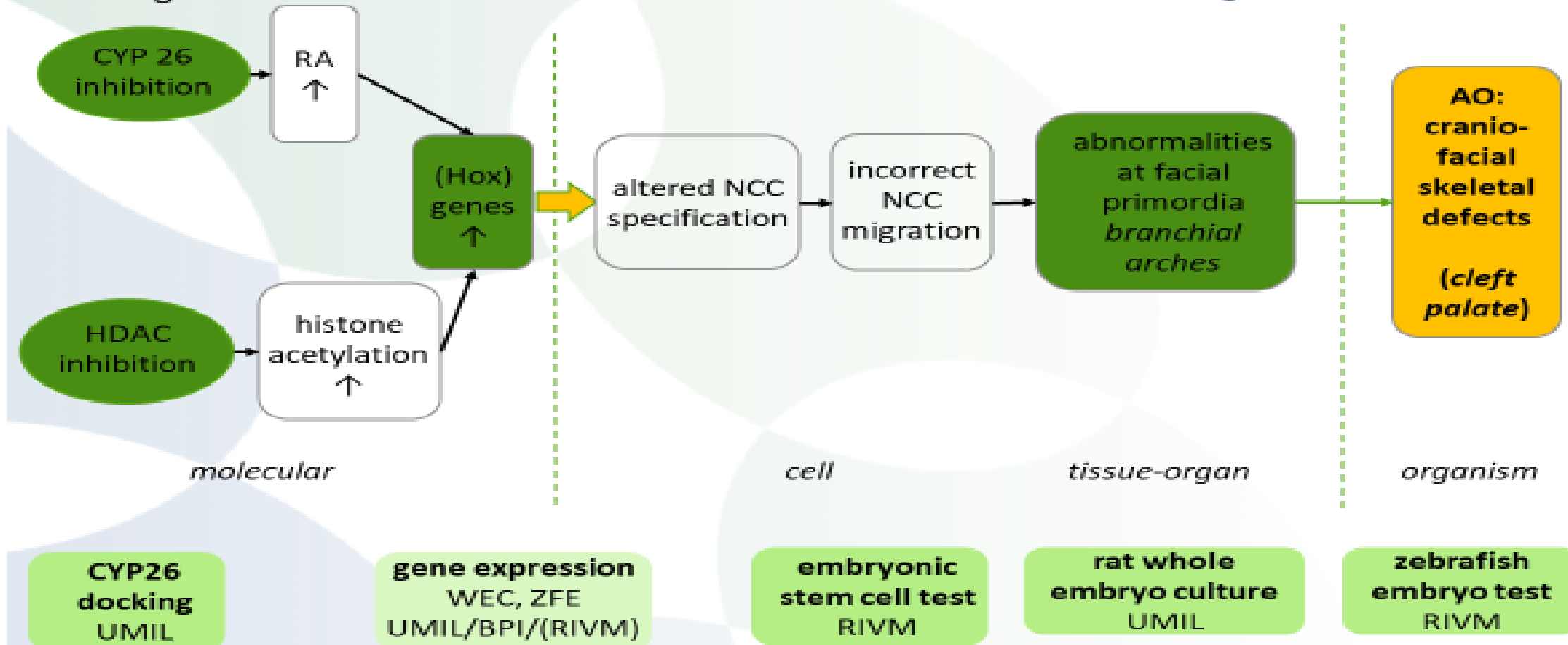
Brussels, Belgium

By Professor Angelo Moretto, Milane, Italy



Funded by the Horizon 2020
Framework Programme of the
European Union

Disruption of the retinoic acid balance and of histone deacetylase regulated gene expression during embryogenesis leading to craniofacial defects



Summary EST-WEC-ZFE

1	2	MoA	EST	WEC	ZFE
Cyproconazole	flusilazole	similar	Dose-addition	Dose-addition	Dose-addition
Triadimefon	thiram	dis-similar	X	x	Infra-additive
Cyproconazole	TCDD	dis-similar	X		Dose-addition
Triadimefon	TCDD	dis-similar	x		Dose-addition
Cyproconazole	fenpropimorph	dis-similar	Infra-additive		Dose-addition
Triadimefon	PFOS	dis-similar			Dose-addition
Triadimefon	endosulfan	dis-similar			Dose-addition
Triadimefon	prochloraz	dis-similar		No Dose-add.	Dose-addition
Cyproconazole	EE2	dis-similar	Dose-addition		
Cyproconazole	dinitrophenol		Infra-additive		
Cyproconazole	endosulfan		Dose-addition		
Cyproconazole	ethanol	similar		Dose-addition	
Triadimefon	ethanol	similar		Dose-addition	
Cyproconazole	traidimefon	similar	Dose-addition	Dose-addition	Dose-addition
Cyproconazole	valproic acid	dis-similar	Dose-addition	Dose-addition	Dose-addition
Triadimefon	Valproic acid	dis-similar	Dose-addition	Dose-addition	Dose-addition

The methodology offers a high level of protection and allows the application of the precautionary principle

Thank you

Thank you for your attention

Questions and comments welcome!



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