Methodologies for grouping agrochemicals for cumulative risk assessment (CRA)

G. Semino –Beninel, Bayer CropScience

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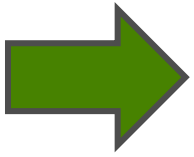
Outline

- Background
  - Legal requirements in EU for agrochemical
  - Ongoing initiatives
- EFSA approach for Cumulative Assessment Groups (CAGs)
  - Thyroid CAGs
  - Nervous system CAGs
- Refined approaches
  - Allocation of compounds to CAGs
  - Streamline subgroup number in CAGs
- Additional considerations on mixture interaction
- Conclusion

Toxicity studies for agrochemical in EU

Toxicity studies are required with the active ingredient

Toxicokinetics and metabolism
Acute oral, dermal, inhalation, skin and eye irritation, skin sensibilisation, phototoxicity
Genotoxicity
Repeated short & long term toxicity, carcinogenicity
Developmental and reproductive toxicity
Neurotoxicity
Mechanistic and/or complementary studies (hepatotoxicity, ED properties, metabolites)
Literature data, medical data, epidemiology



Reference values for dietary
(ADI, ARfD)
&
non-dietary (AOEL, AAOEL)
Risk assessment

Legal requirements for Cumulative Risk Assessment (CRA) of agrochemical in EU

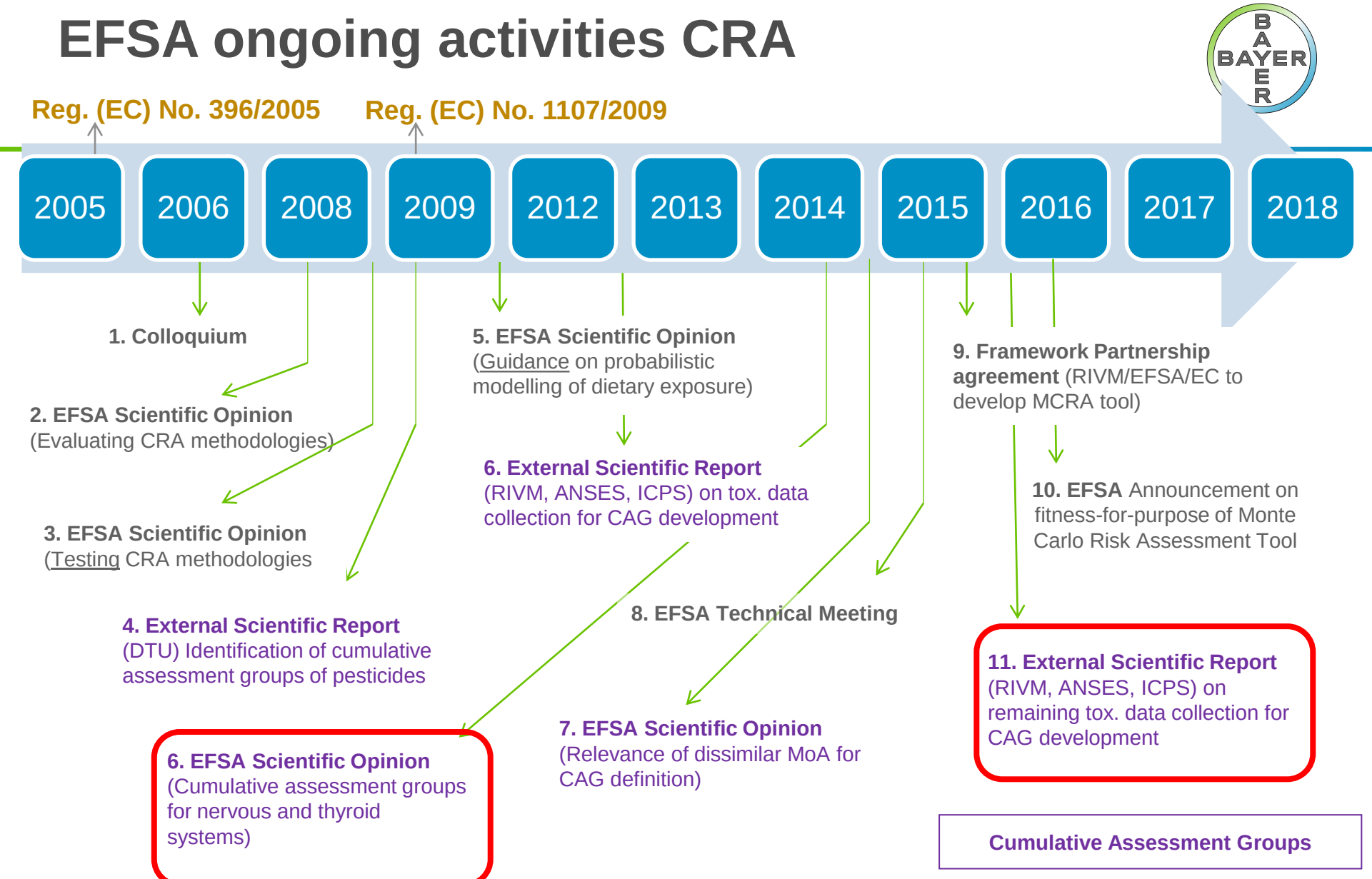
- Regulation (EC) No. 396/2005 on Maximu… …ls (MRLs) of pesticides in or on food and feed … **and synergistic effects of pesticides … account for dietary risk assessment when *ap… …ethodologies* are available.**

- Regulation (EC) No. 1107/2009 c… …nt protection products on the market … residues of the plant protection products **shall … harmful effects on human health**, taking into account … **…ulative and synergistic effects** where the **scientific methods** accepted by the Authority **to assess such effects are available**

EFSA activities on exposure and dietary assessment

EFSA activities on Cumulative Assessment Groups (CAGs)

EFSA ongoing activities CRA



EFSA grouping approach

Pesticides that produce common adverse outcomes on the same target organ/system should be grouped together in the same Cumulative Assessment Group (CAGs)

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

Any effect in any study, dose level or species

EFSA exclusion approach

The methodology comprises four main steps as follows:

- Identification of the specific effects by:

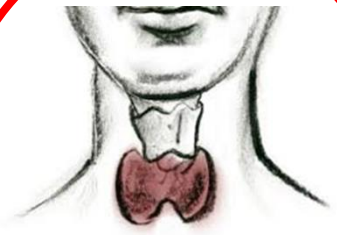
  i) exclusion of local effects
  ii) exclusion of non-adverse effects
  iii) exclusion of effects not relevant to humans
  iv) evaluation of the unambiguous nature of the effect
  v) identification of non-specific effects

- Characterisation of the specific effects
- Data collection
- Grouping of pesticides into CAGs

Page 4 of EFSA Scientific Opinion 2013

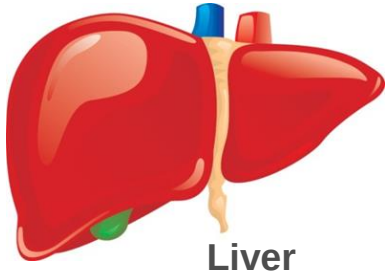
Non-application of exclusion consideration
→ high number of compounds in each CAG

Target organs CAGs from 2013 & 2016 external scientific reports

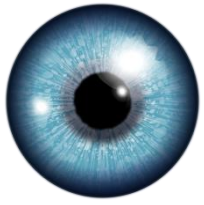


Thyroid
(149/416)

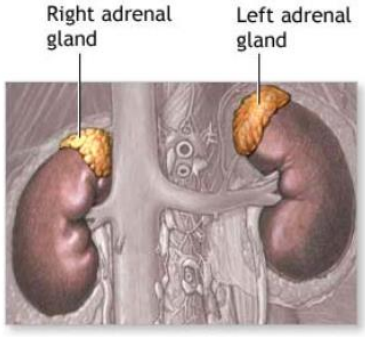
Nervous system
(135/416)



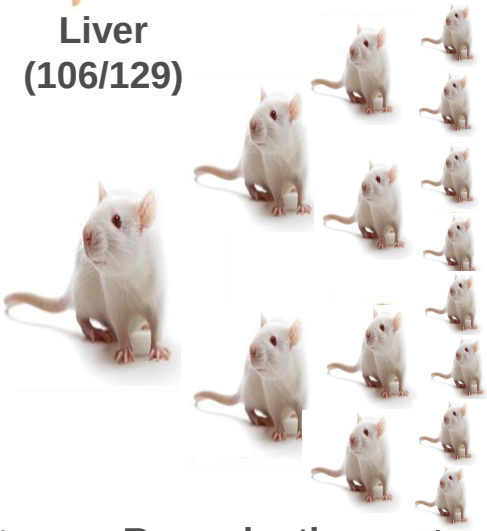
Liver
(106/129)



Eye
(79/416)



Adrenals
(96/416)



Developmental system

Reproductive system

(124/129)

= CAGs already in the 2013 external scientific report

Nervous system CAG

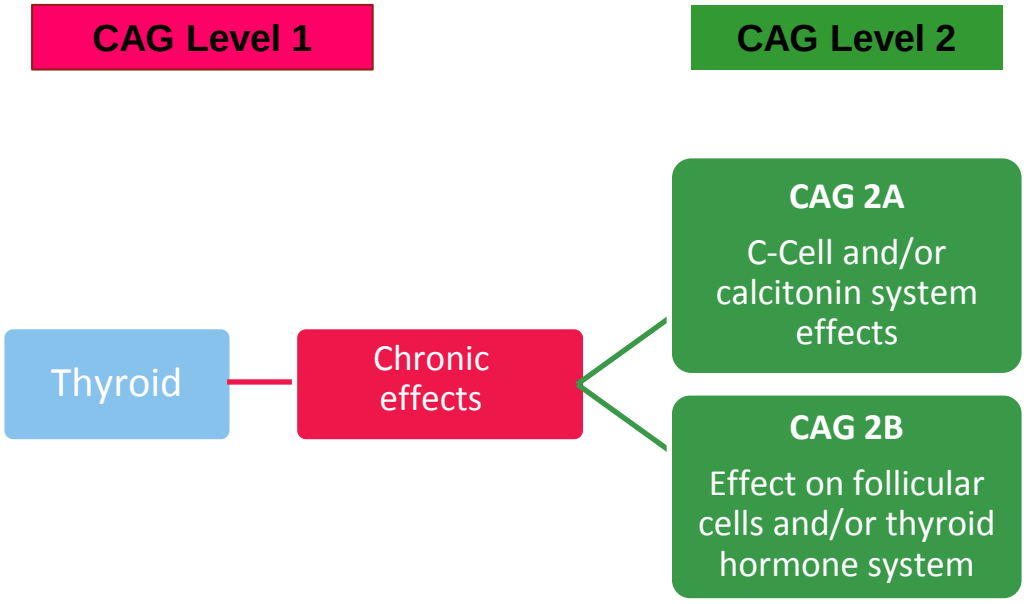
CAG 1 level	CAG 2 level			CAG 2 level		
	Acute exposure	Scientific Opinion 2013	External Scientific Report 2016	Repeated exposure	Scientific Opinion 2013	External Scientific Report 2016
Nervous system	Autonomic division	28/287	16/129	Autonomic division	24/287	16/129
	Sensory division	19/287	17/129	Sensory division	21/287	19/129
	Motor division	42/287	33/129	Motor division	51/287	41/129
	Neurochemical effects	13/287	17/129	Neurochemical effects	15/287	33/129
	Neuropathology	Not defined	2/129	Neuropathology	18/287	15/129
	Developmental neurotoxicity	Not defined	1/129	Developmental neurotoxicity	Not defined	6/129

Overall **135** compounds out **416** were included (one a.i. belonging to more than one subgroup)

Evaluation by ECPA - examples

Substance	CAG 1	CAG 2	Result summary	Remark
Fluopyram	Nervous system acute	Motor division	Hypo-activity was suggested, but there was no evidence for acute neurotoxicity in the other studies (including repeated neurotoxicity) at the same dose levels	Inappropriate grouping
Fluquinco-nazole	Nervous system acute	Motor division	Tremor was seen in 28-day study at day 9 the earliest → to be considered for grouping in chronic	Inappropriate grouping

Thyroid system CAG



	Scientific Opinion 2013	External Scientific Report 2016
CAG 2A	22/287	10/129
CAG 2B	96/287	53/129

Overall **149** compounds out **416** were included (one a.i. belonging to more than one subgroup)

Were all the compounds allocated to this CAG appropriately ?

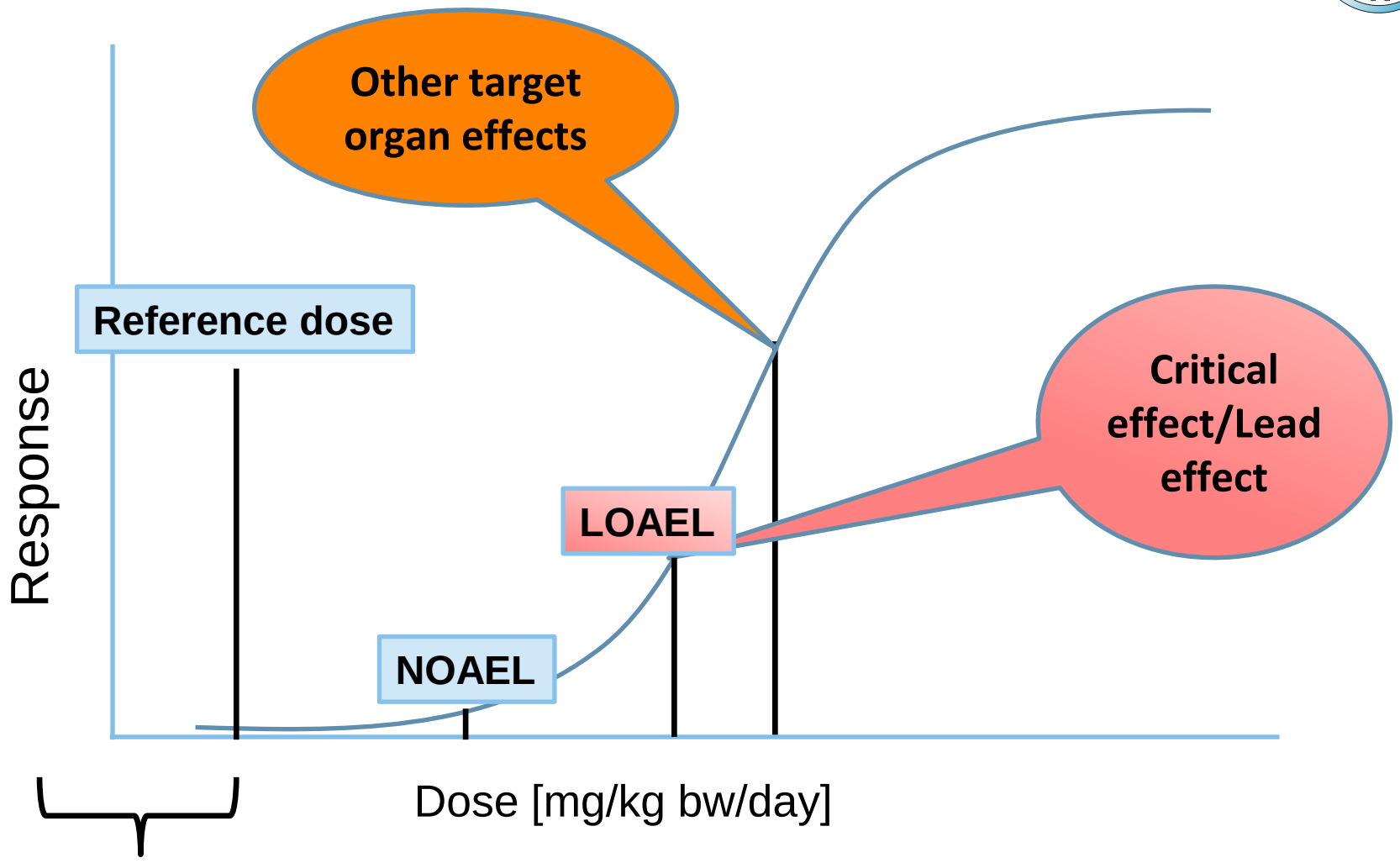
ECPA evaluation - examples

Substance	CAG 1	CAG 2	Result summary	Remark
Bitertanol	Thyroid	2B	Thyroid weight↑; thyroid enlargement in 28-day rat study only, no histopathology; no thyroid toxicity in longer term rat studies or in other species	No evidence for thyroid toxicity
Fluxapyroxad	Thyroid	2B	Thyroid toxicity seen in several rat studies; not in other species; clear evidence for indirect (to liver toxicity) mechanism from studies	Indirect not human-relevant mechanism

ECPA proposal for grouping

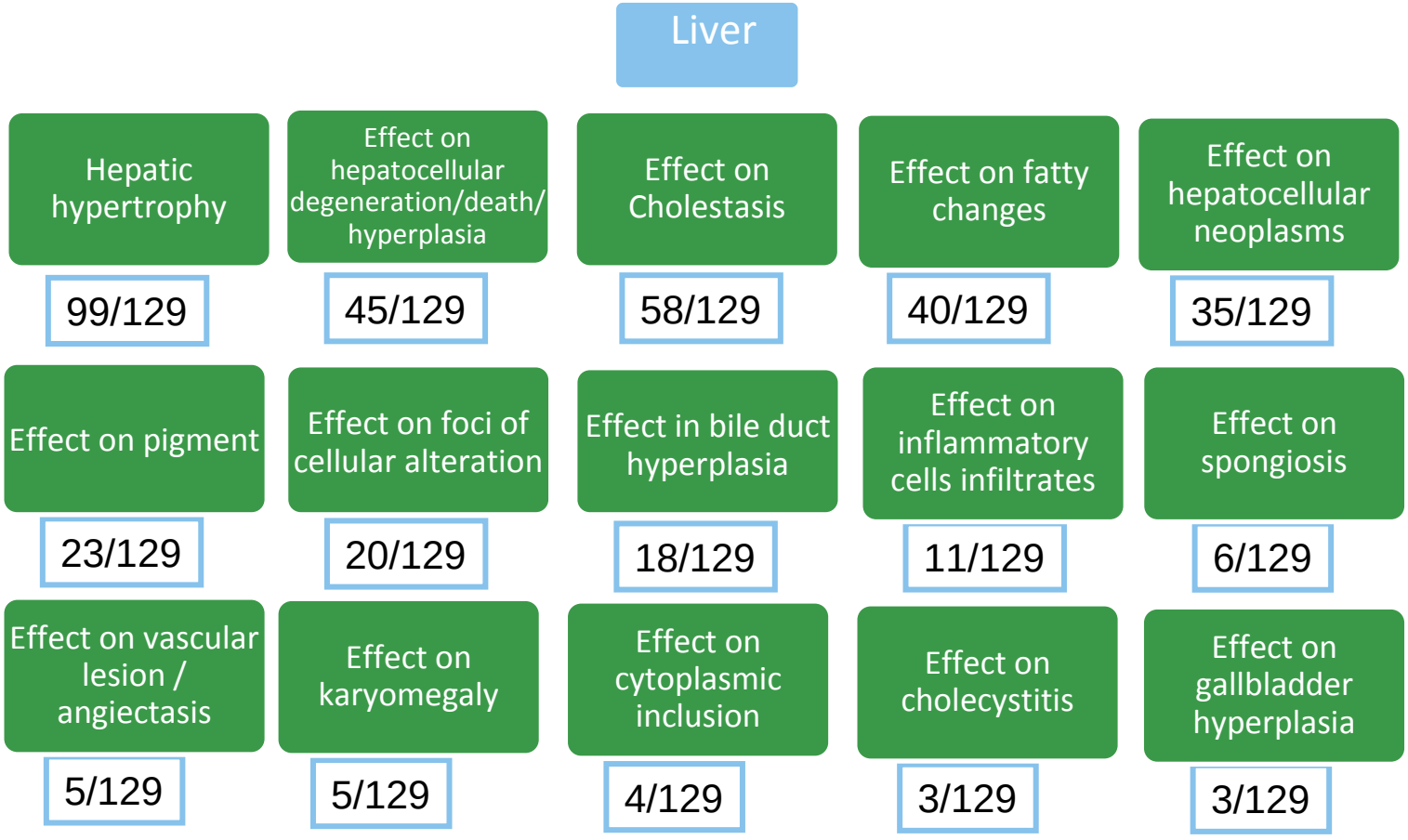
- ✓ Effects should be treatment-related
- ✓ Effects should be adverse
- ✓ Weight-of-evidence should indicate that the target organ is really affected
- ✓ Mode of action information shall be applied more stringently → human relevance
  - Species-specific target-organ effects are not relevant for human safety assessment
  - Therefore, species-specific target-organ effects are not relevant for CAG assessment
- ✓ Effects seen at high doses and/or effects secondary to general systemic toxicity only shall not be used for grouping

Lead or Primary effect



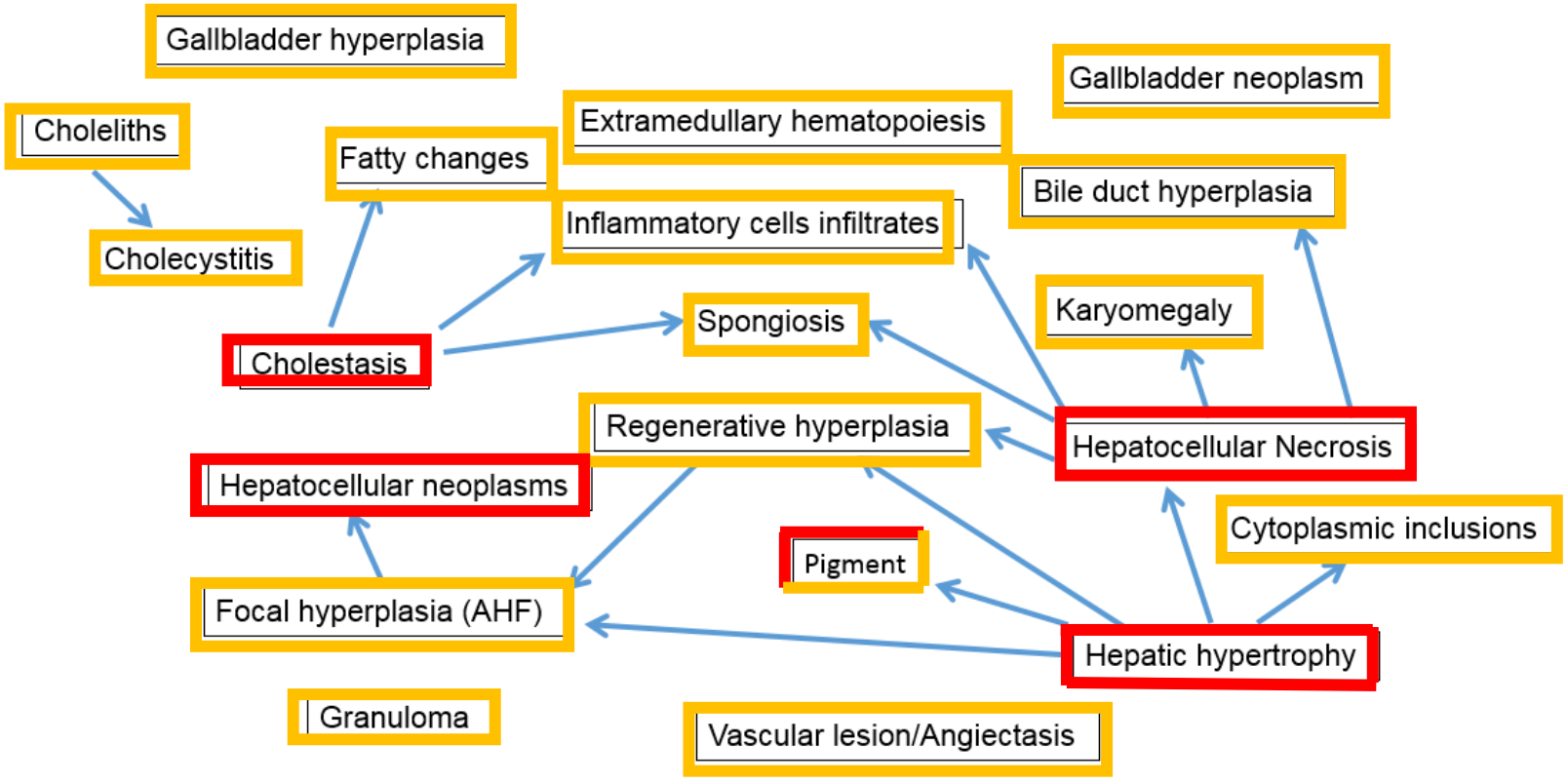
Estimated human exposure levels

External Scientific Opinion 2016: Proposal for Liver Groupings



A total of 106 compounds out 129 and 15 subgroups: does this make sense?

Exploring the Liver Grouping



Refinement of Liver Grouping

- Chemicals have been assigned to the broad range of pathological endpoints irrespective of whether or not that endpoint was a **primary response** to the given chemical or occurs as a **secondary consequence** of the pathology resulting from **other primary endpoints**.

Primary endpoint
It provides mode of action information on a given chemical that allows those possessing **common modes of action** to be correctly grouped under that particular primary pathological endpoint or CAG level.

Secondary endpoint
A secondary pathological endpoint is one that can **develop from a number of different primary pathological endpoints** and provides no information on a common mode of action of the grouped chemicals.

Refinement based on appropriateness of the nomenclature and Interlinks between effects triggered by common mode of action

Possible interactions among chemicals

Antagonism or
Synergism
Rarely observed

Independent action
Toxicity dominated by the toxicity of individual chemicals

Dose/concentration addition
Might occur when the chemicals share the
same mode of action
and/or target

Additivity of the effects is the general guiding principle

Possible interactions among chemicals

- For data poor situations, dose addition could be used as default option

- Refinement with physiologically based modeling to:
    a. calculate the biologically effective dose of the mixture components at the target tissues
    b. Incorporate information on absorption and enzyme saturation
    c. Investigate the dose-response ranges

Conclusion

- External Scientific Opinion 2016 and data collection from 2013 needs to be revised
- Key fundamental issues that need to be addressed:
  - Critical refinement of grouping criteria (*e.g.* liver) and re-evaluation of compounds
  - Appropriate allocation to a CAG by following the weight of evidence approach and considering consistency of the effects seen in the different studies/ species/ doses
  - Exclude substances with no lead effect, as only the lead effect is relevant at the exposure levels to be assessed
  - Explore the possible interactions among chemicals incorporating pharmacokinetics and pharmacodynamic information

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Science For A Better Life

Thank you for your attention!