



The assessment of chemically defined flavourings: the experience so far

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Barcelona, 6 May 2015

OUTLINE

- Part I - P. Manini
 - The assessment of food & feed flavourings
 - Where we are: Some figures on the work done (and on what remains to be done)
- Part II - C. Hogstrand
 - Safety assessment of flavourings

FOOD & FEED FLAVOURINGS

Food flavourings (~2700 substances)

- Flavouring evaluation programme (Reg. 1575/2000)
- EU list of flavouring substances (22 October 2012)
- JECFA and EFSA applied a tiered approach, named 'the Procedure', to the assessment of food flavours

Feed flavourings (~600 substances)

- According to Regulation (EC) 429/2008, a **limited procedure** is allowed for substances already approved for use in human food (if the food safety assessment is relevant to the use in feed)



THE STARTING POINT (1)

The FEEDAP assessment of feed flavourings is based on the CEF/JECFA assessment of the same substances as food flavours **providing that**

- substances are included in the EU list of food flavours (Regulation EU 872/2012)
- same specifications for food/feed flavourings
- substances are not genotoxic
- substances do not give rise to safety concerns at the **level of dietary intake**, estimated on the basis of the Maximum Survey Derived Intake approach

THE STARTING POINT (2)



- A full dataset is needed for the assessment of substances
 - ❑ not included in the EU list
 - ❑ not assessed as food flavours (CEF/JECFA)
 - ❑ with different specifications (food/feed)
- For substances **no longer used** as food flavours, the application was withdrawn (e.g. dimethyl tetrasulfide CG 20, geranyl acetone CG 5)

SPECIFICATIONS OF FOOD/FEED FLAVOURINGS

Characterisation of feed flavourings

- Data on **five batches** are requested to demonstrate compliance with specifications set for food flavours
- In some cases, data on purity for one batch was accepted (low production volumes, low use levels, JECFA specifications met)
- In the lack of data on purity, the FEEDAP Panel was unable to perform an assessment (13)



GENOTOXICITY

- If the CEF Panel has raised (geno)toxicity concerns for a substance and requested additional toxicity (5) or genotoxicity data (43)
 - The FEEDAP Panel will not proceed with the assessment until the issue has been resolved
- If the CEF Panel concludes that a substance is genotoxic (e.g. 3-acetyl-2,5-dimethylthiophene)
 - The FEEDAP Panel will consider the substance unsafe for target species, for the consumer of animal products, and for the user (CG 29; EFSA, 2013)

USE LEVELS IN FOOD AND FEED

- Safety of food flavours is assessed at the level of dietary intake estimated by the MSDI approach
- Use levels in feed are typically **much higher** than the corresponding use levels in food
- Definition of “**normal and high use levels**” based on marketed volumes (2006), the assumption that only 10% of compound feed contain the flavouring, and categorisation into three groups (1, 5 and 25 mg/kg)
- Unclear how “normal and high use levels” relate practical to conditions of use



CONDITIONS OF USE: USE IN WATER

The use in water for drinking

- Flavourings are volatile compounds
- Many compounds are insoluble or slightly soluble in water ($\text{LogK}_{\text{ow}} > 2$)
- No data on the short-term stability in water (e.g., degradation due to microbial activity)
- No specific proposals for the dose used in water
- The FEEDAP Panel cannot conclude on this route of administration



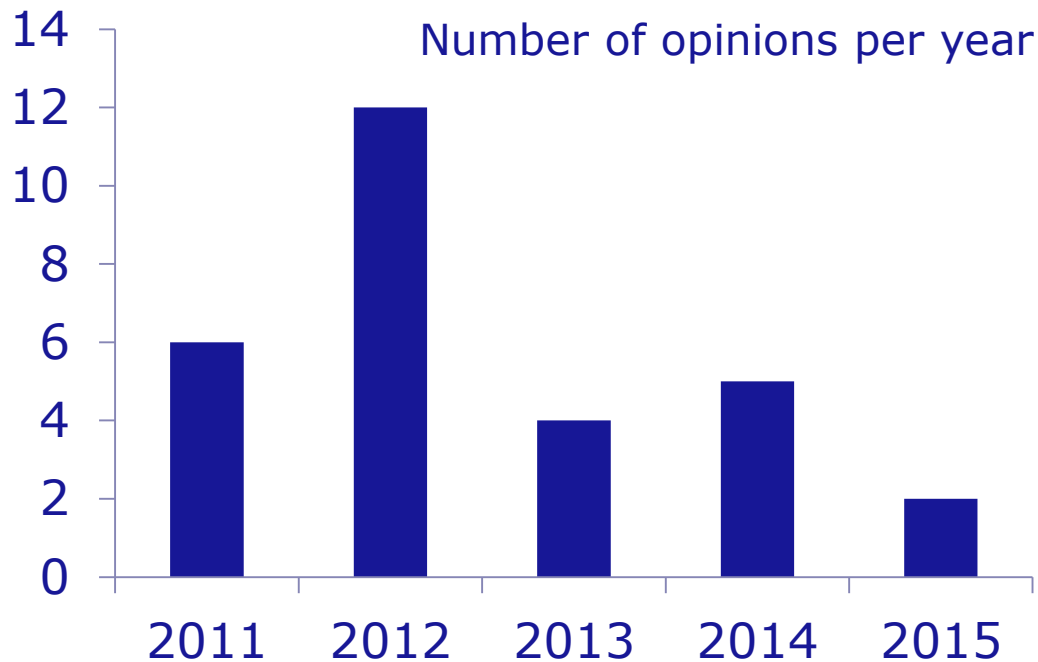
APPLICATIONS RECEIVED/OPINIONS ADOPTED

No. of applications: 41

- 30 (+1) CDGs
- 8 stand-alone dossiers
- 2 mixtures

Opinions adopted: 29

- 27 for re-evaluation
- 1 mixture (Art. 4)
- 2 'partial' opinions
- 2 opinions for the same application

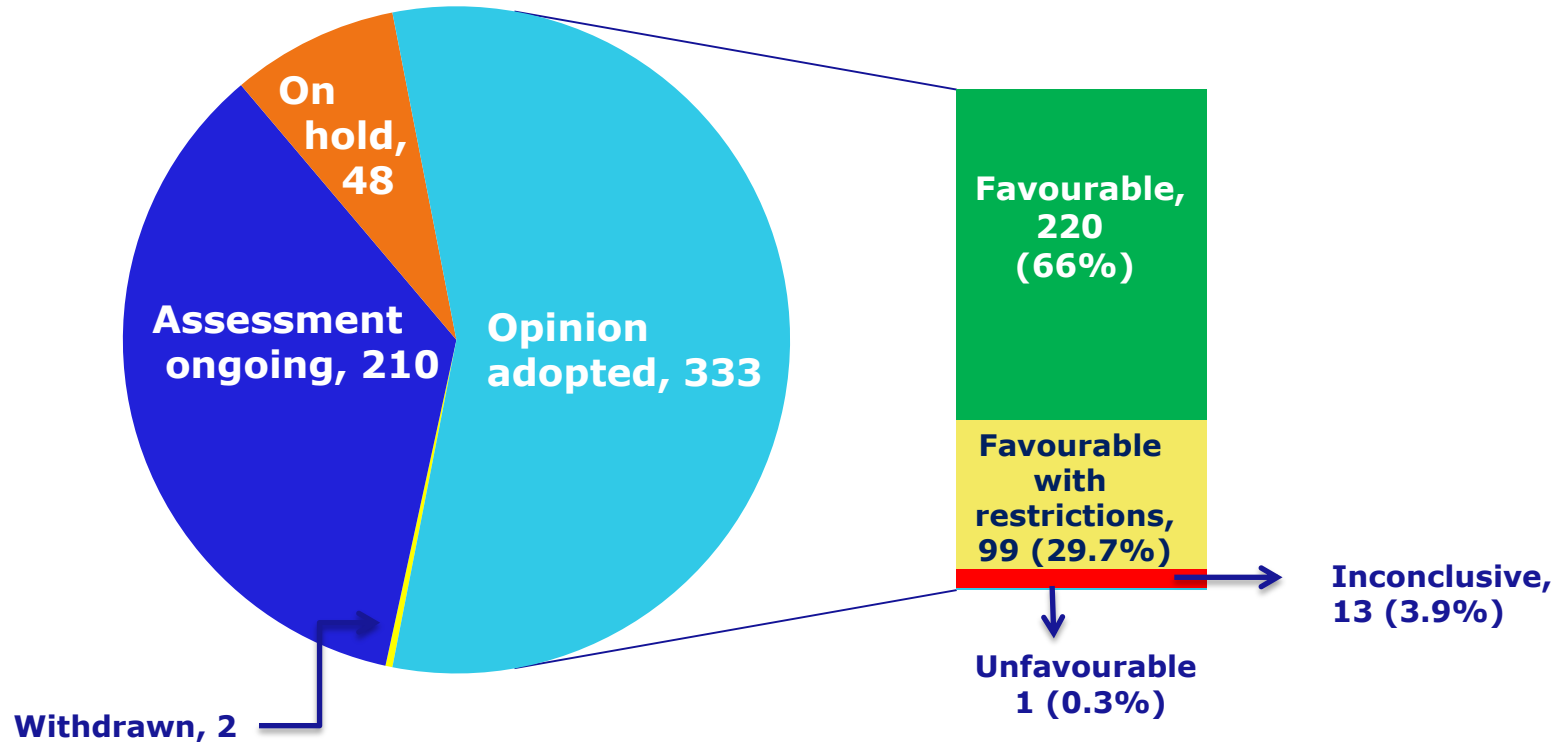


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FLAVOURING ADDITIVES: WHERE WE ARE

No. of substances: 593 + 2 mixtures

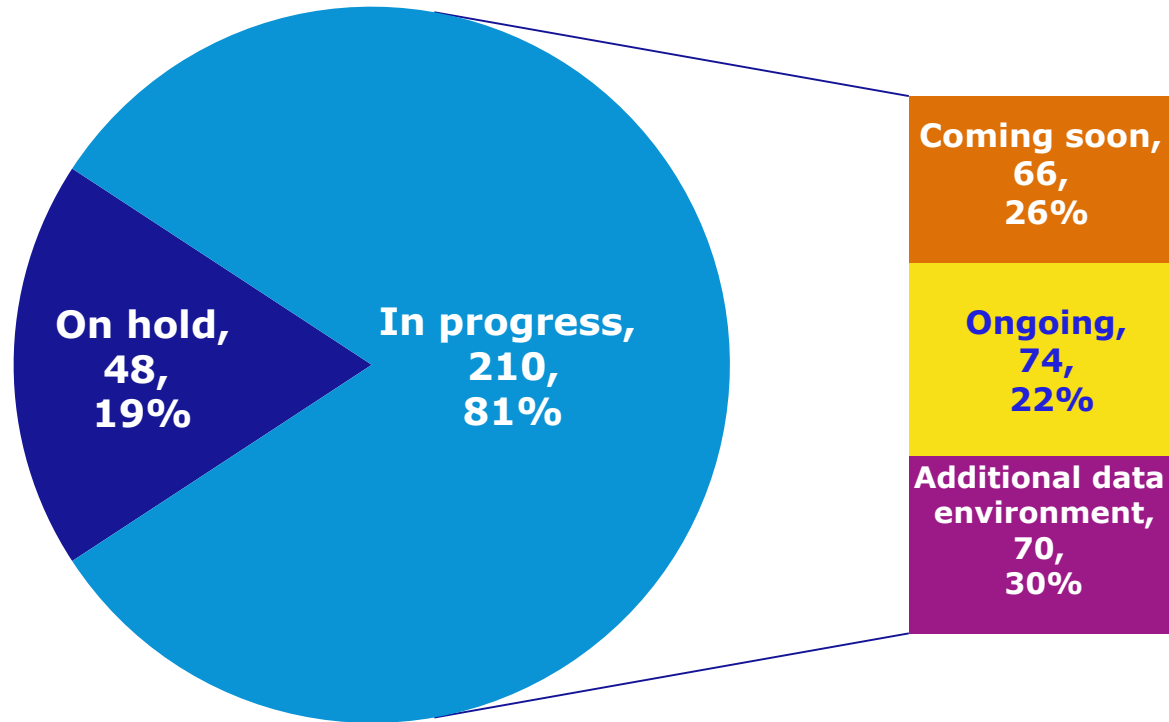
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WHERE WE ARE GOING TO

No. of substances: 258 + 1 mixture

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No. of applications: 17
(258 substances)

- ❑ 14 (+1) CDGs
- ❑ 1 stand-alone dossier
- ❑ 1 mixture

priority to the groups with less compounds 'on hold'

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THE SAFETY ASSESSMENT

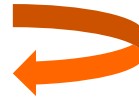
Main constraints in the assessment of feed flavourings - Lack of data on:

- Safety for target species (tolerance studies)
- Metabolism of flavourings in the target species
- Residues in products/tissues of animal origin
- Skin and eye irritancy, skin sensitisation
- Environmental fate and ecotoxicity

TARGET SPECIES: STEPWISE APPROACH

For additives **already authorised for use in food**,
a comparison with human intake from food
(expressed as metabolic bw)

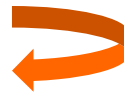
Tier 1



If animal intake is **higher than human intake**,
or the additive is **not authorised** for use in food

- the lowest NOAEL
- the benchmark dose (BMD) procedure
- the threshold of toxicological concern (TTC)

Tier 2



Tolerance studies

Tier 3

SAFETY FOR TARGET ANIMALS: TIER 1

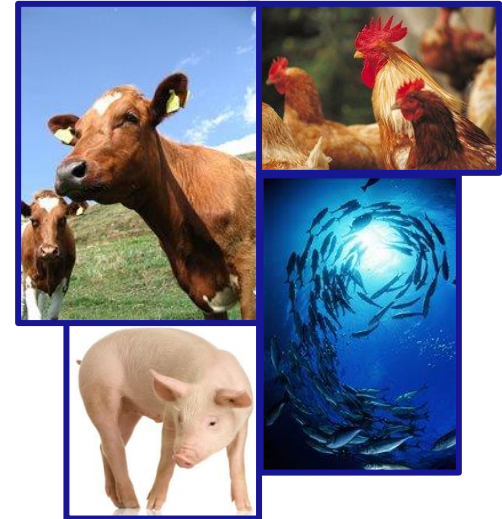
Feed flavourings are considered safe for all animal species without restrictions (69 substances)

- If the **use levels** in target animal species are \leq the use levels considered safe in humans (6)
- If the same substances are used as **feed additives** at higher concentrations (e.g. organic acids 4, and related compounds 16)
- If substances are considered **nutrients** (fatty acids and esters 11, aminoacids 19) or components of **cell metabolism** (dicarboxylic acids and esters, 13)



SAFETY FOR TARGET ANIMALS: TIER 2

- Safety is extrapolated from toxicological data in laboratory animals (NOAEL, BMDL) by applying adequate **uncertainty factors** (UFs)
- When a full toxicological dataset is available, the extrapolation from laboratory animals to target species needs an UF of 100
 - 10x for inter-species
 - 10x for intra-species



SAFETY FOR TARGET ANIMALS: NOAEL

Is the toxicological dataset adequate to derive a NOAEL?

- Minimum requirements for studies in laboratory animals: sub-chronic, repeated-dose studies, performed with the substance under assessment, multiple doses tested, multiple endpoints assessed
- Studies showing major limitations in conduct and reporting were not accepted
- In some cases, studies with only **one dose** tested were accepted (depending on quality of the study, end-points measured, outcome, etc.)

SENSITIVE SPECIES

Chemical formulations containing eugenol and isoeugenol are used in water as an **anaesthetic** for fish, crustaceans and amphibians

- The use of isoeugenol (CG17), eugenol and eugenyl acetate (CG 18) as a flavours in feed for fish and other aquatic species is contraindicated



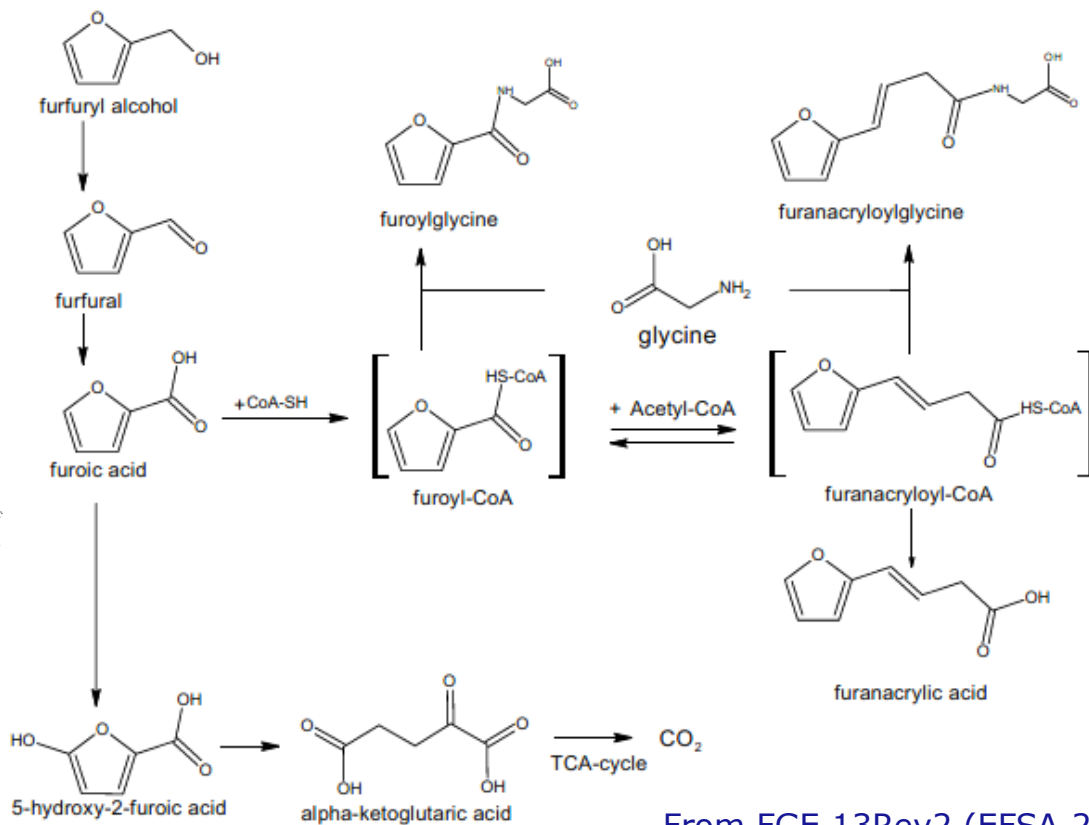
READ-ACROSS BETWEEN SUBSTANCES

Extrapolation from one substance to other chemically related substances (belonging to the same **Flavouring Group evaluation**), e.g. setting of a group NOAEL for all flavourings belonging to the same Chemical Group

- As a general rule, this is not a satisfactory approach
- Possible in some limited cases and could apply to:
 - alcohol/ester, thiol/thioester pairs
 - substances sharing common metabolic pathways (interconverted by hydrolysis, oxidation/reduction reactions)



EXTRAPOLATION: ONE EXAMPLE



The NOAEL for furfural could potentially be extrapolated to furfuryl alcohol, furfuryl acetate, and methyl 2-furaote, as the substances share common metabolic pathways and are interconverted by hydrolysis and oxidation/reduction reactions

From FGE.13Rev2 (EFSA 2012)

A PARADOXICAL OUTCOME

- Toxicological data are usually not available for substances with perceived low toxicity
- In the lack of data, the threshold of toxicological concern (TTC) approach is applied
- Similar approach followed for food flavours
- **Paradoxical outcome:** the application of TTC results in lower safe concentrations in feed for substances that may have low toxicity compared to more toxic substances, for which toxicological data exist



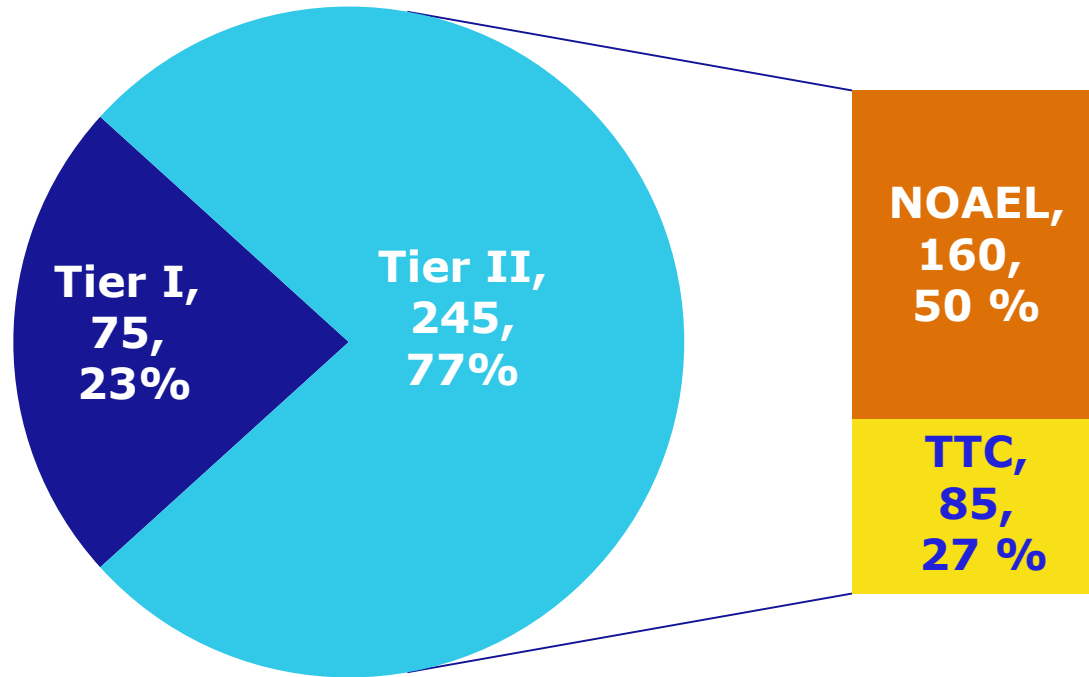
SAFETY FOR TARGET SPECIES: CONCLUSIONS

The FEEDAP Panel concluded that:

- The use of a feed flavouring is **safe** at the proposed use levels ("normal and high levels") for all animal species (220 flavourings)
- When the calculated safe level is lower than the proposed use levels, the Panel set a **maximum content in feed** which corresponds to the calculated safe level in feed (99 flavourings)

SAFETY FOR TARGET SPECIES: THE OUTCOME

Last update : April 2015



SAFETY FOR SPECIES: WHICH WAY FORWARD?

- In the lack of data, conservative assumptions are made and related uncertainties need to be accounted for by the use of adequate uncertainty factors, resulting in conservative outcome
- To reduce the conservatism, data on the safety for target species are needed
- Tier 3: Tolerance studies?

TOLERANCE STUDIES

The additive has to be SAFE for the target animals

Tolerance studies

A limited evaluation of the **short-term toxicity** of the additive for the target animals is used to establish a **margin of safety**

- Multi-fold overdose of the product (10x, 100x)
- Control production, health, gross pathology and blood haematology and chemistry (**limited endpoints**)



SAFETY FOR THE CONSUMER

The basis for the assessment of consumer safety

- The same compounds have been assessed as food flavours and are authorised without limitations
- In humans and rodents, compounds are extensively metabolised and excreted, or enter the metabolic pathways for endogenous biomolecules
- Mammals, birds and fish share a similar metabolic capacity to handle the compounds (the enzymes involved in the metabolism of the flavourings are expressed/present in target animals)

SAFETY FOR THE ENVIRONMENT (1)

Tiered approach: an environmental risk assessment (ERA) is **not needed** when:

- The natural occurrence of the compounds in the European environment is higher than the high proposed level in feed
- The additive is intended for non-food producing animals only
- The compounds are extensively metabolised by the target species and excreted as metabolites of no environmental concern

Guidance on environmental risk assessment
<http://www.efsa.europa.eu/en/efsajournal/pub/842.htm>

SAFETY FOR THE ENVIRONMENT (2)

Tiered approach: ERA is used

- Conservative when limited or no data are available
- Phase I: Modelling of Predicted Environmental Concentrations (PEC), based on physico-chemical characteristics (K_{OC} , vapour pressure, solubility) obtained from the SMILE notation of the substance (EPIWEB)
- Phase II: Estimation of EC50 for earthworm, fish, algae and Daphnia from the SMILE notation (ECOSAR)
- Uncertainty factors are applied to modelled parameters (e.g. 1000 to the lowest EC50)
- More data → less uncertainty → less conservatism in the assessment

SAFETY FOR ENVIRONMENT: THE OUTCOME

Feed flavourings do not pose a risk to the environment when used at the concentrations considered safe for target species:

- at the proposed conditions of use (207 compounds)
- at the calculated maximum safe feed concentration (98)

With few exceptions:

- 5 compounds - safe at reduced levels
- 10 compounds - safety to aquatic compartement could not be established



EFFICACY

Efficacy of feed flavourings does not need to be demonstrated if

- the compounds under assessment are used in food as flavours
- their function in feed is essentially the same as that in food
- no other claims, such as increased palatability, are made



Thank you
for your attention!