Assessing safety of feed flavourings for target species: the testing of mixtures

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FUNDAMENTAL ISSUES

- How mixtures should be formulated
- Ensuring delivery of the intended dose
- Palatability
- Extrapolation of results to other (all) target animals
- Extrapolation of results to other compounds not included in the mixture tested

MIXTURE FORMULATION

Mixtures of flavourings

The WG discussed different possibilities:

- Flavour formulations to ensure palatability
- Grouping the compounds on the basis of the metabolism/ADME
- Random choice of compounds

DOSES

Doses

- The WG had no concerns on the range of doses proposed to be tested in tolerance studies
- The conclusions will be for each single compound considering the doses tested for that compound
- If applicable, margins of safety will be determined considering the highest dose tolerated and the maximum use level proposed for each compound

DOSES

Doses

- Due to the volatile nature of the compounds the actual amount ingested of each flavouring compound is unknown
- Consequently safe doses cannot be established

PALATABILITY

Palatability

- With the administration of the compounds presented in the pilot trial is not possible to determine whether an observed **reduction in feed intake** is a palatability or a metabolic issue
- Any palatability issue could be avoided by the use of **microencapsulation**

DOSES AND PALATABILITY

Microencapsulation

- Would ensure delivery of intended dose of compounds of volatile nature
- Would prevent decreased feed intake due to a possible palatability issue

CONCLUSIONS FROM STUDIES WITH MIXTURES

Which conclusions on **safety** from studies using **mixtures** of several flavourings?

- If a mixture is tolerated, then safe levels in feed for **piglets** can be derived for each compound included in the mixture
- If adverse effects are observed at any of the doses tested, then **all** compounds included in the mixture will be considered as raising concerns on the safety for target species

EXTRAPOLATION TO ALL ANIMAL SPECIES

Extrapolation

- Extrapolation to “all animal species” can be only applied when tolerance studies are performed on three major species with a sufficient margin of safety
- Different species have different sensitivities, so extrapolations cannot be easily done to all animal species
- If studies proposed are conducted only with weaned piglets, the results can be extrapolated to pigs, but not other species

EXTRAPOLATION TO OTHER COMPOUNDS

Extrapolation to other non-tested flavourings

- In general, the Working Group will be able to conclude only on the compounds included in the mixture tested
- Read across to another compound with similar chemical structure and/or metabolism is an exception rather than the rule

TYPE OF STUDY

Tolerance *versus* toxicity study

- A sub-chronic 90-day toxicity study would have several advantages over a tolerance study performed with a single target animal
- Such an approach would allow
  - a **NOAEL** to be derived for each compound included in the mixture
  - **extrapolation** to all animal species
  - accurate **dosing** (by gavage/ microencapsulation)