

EFSA Info Session on Applications

Technical meeting on food flavourings applications

Parma, 20th January 2015



UPDATE FROM THE APPLICANTS

TOPICS



- General procedural & administrative issues
- Risk assessment challenges of toxicological nature, including genotoxicity
- Other scientific challenges: mainly intake & exposure assessment

UPDATE FROM THE APPLICANTS

COLLABORATION WITH EFSA APPLICATION DESK

Industry is perceiving the collaboration with the EFSA Application Desk as very good and effective.

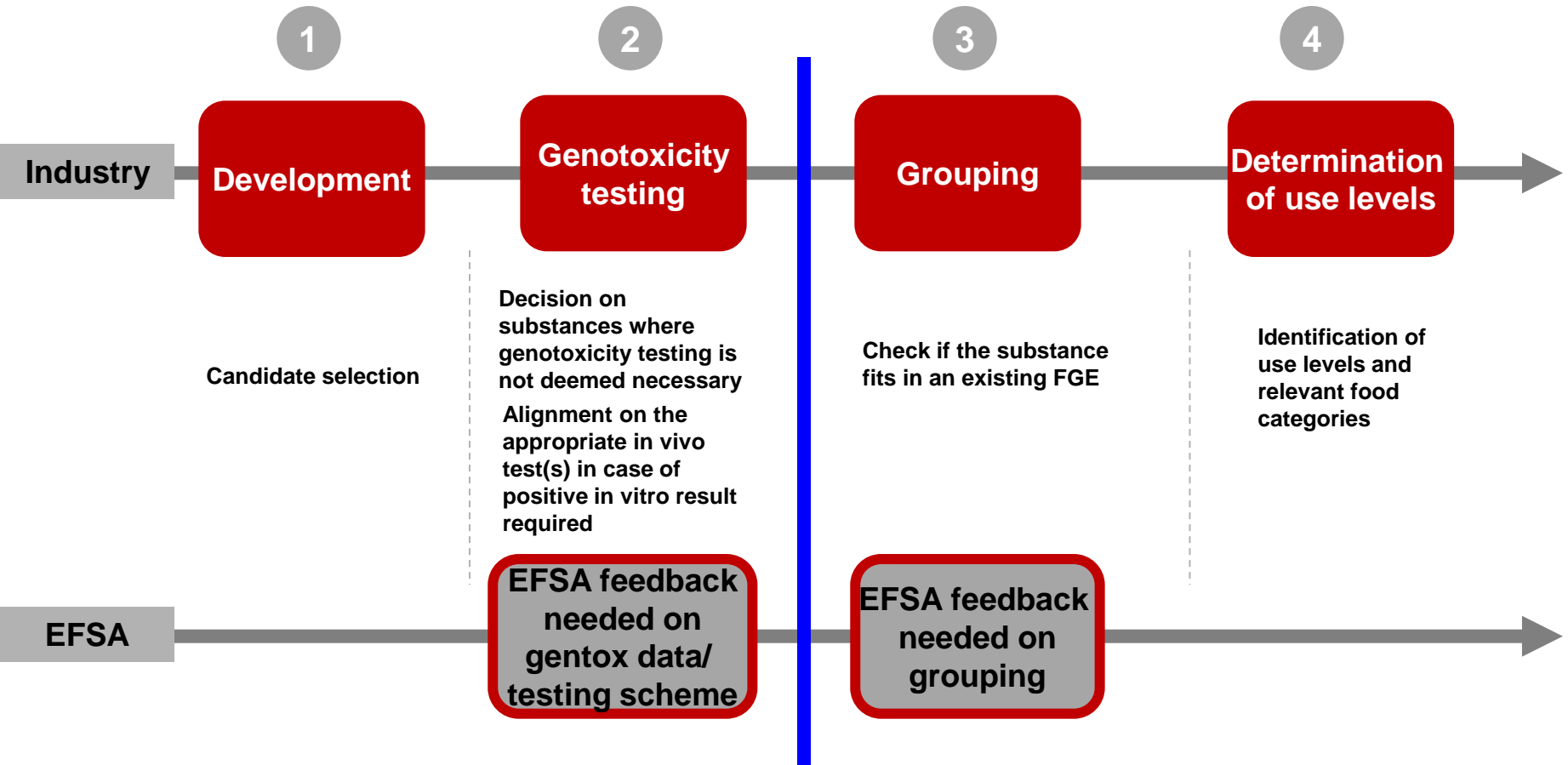
- Clear rules
- Good communication
- Timely confirmations of receipt
- Timely feedback

As already outlined during our meeting in November 2012 industry still believes that there would be a benefit in establishing a type of “pre-registration-feedback” for applicants to improve the dossier preparation and assure that appropriate information (especially Tox Data) is submitted.

Currently there is no procedure in place allowing such a data review, but based on the learnings from the ongoing evaluations (e.g. FGE.19) industry would appreciate upfront guidance by the CEF panel.

UPDATE FROM THE APPLICANTS

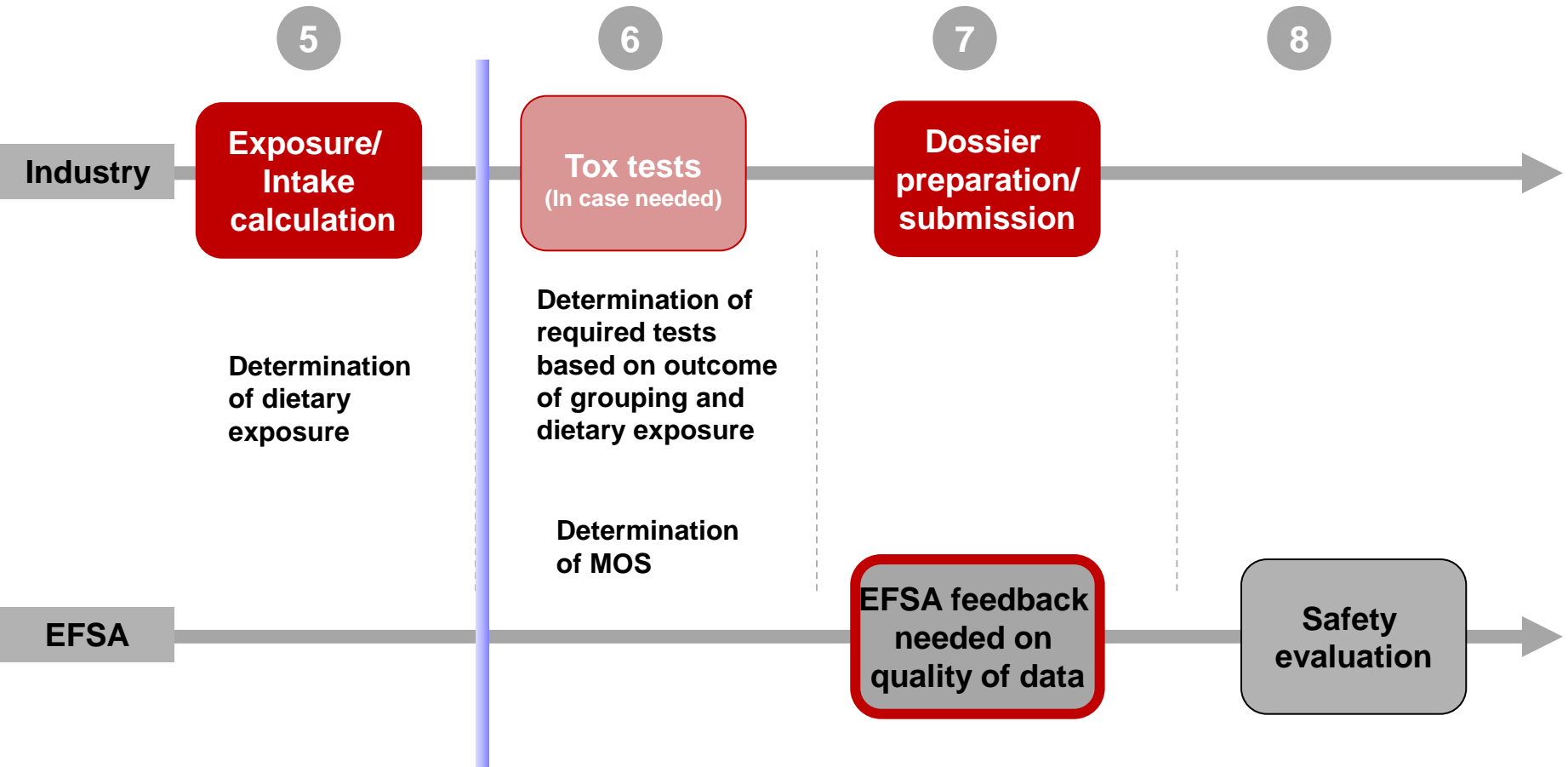
WORKFLOW FROM DEVELOPMENT TO APPROVAL



Critical Milestone
Only substances without genotoxicity concern can move forward

UPDATE FROM THE APPLICANTS

WORKFLOW FROM DEVELOPMENT TO APPROVAL

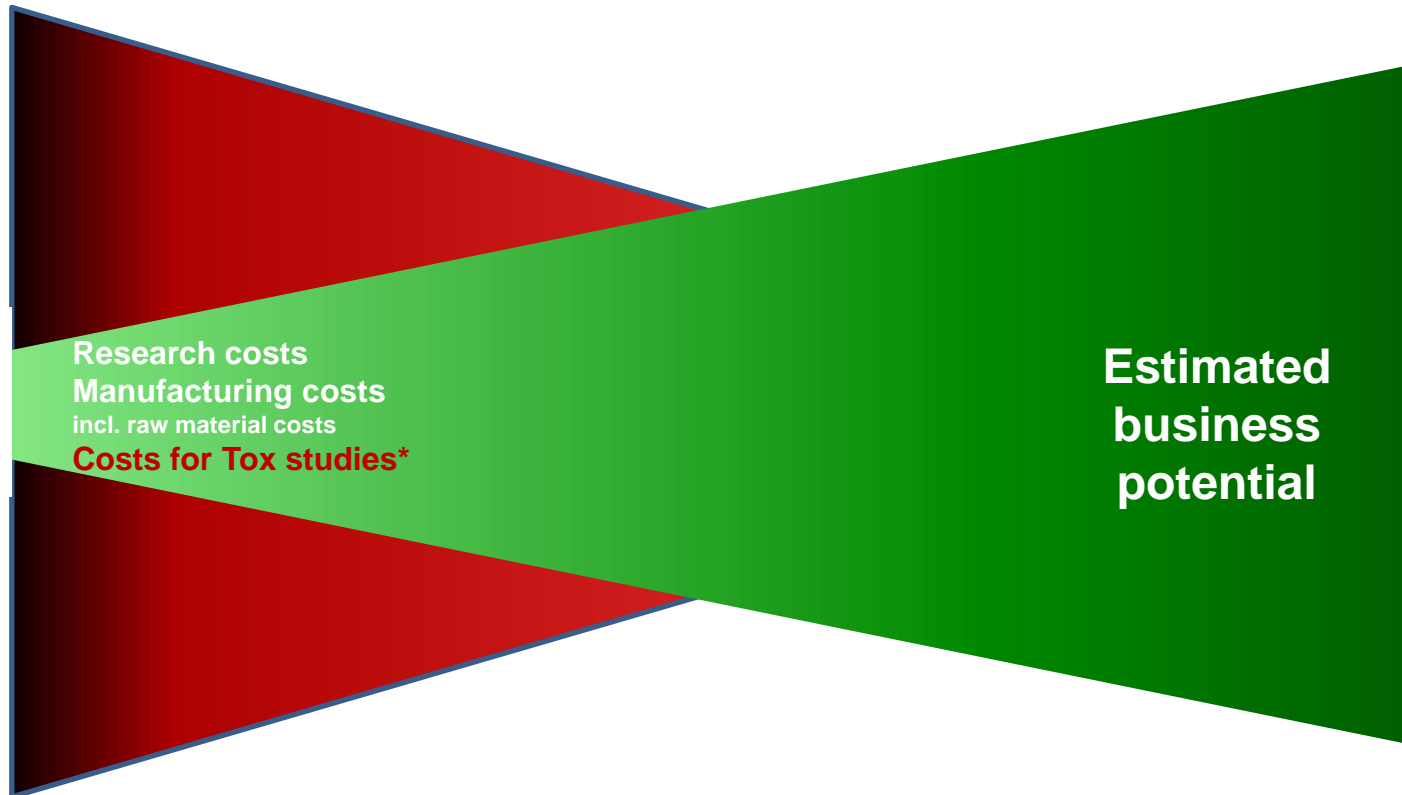


Milestone

Tox Costs might not be covered by the business potential of the new substance

UPDATE FROM THE APPLICANTS

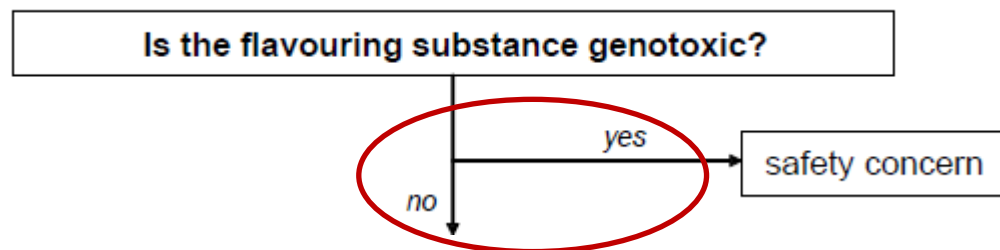
DETERMINATION OF THE RIGHT CANDIDATES FOR REGISTRATION



- New candidates out of the research pipeline are not only identified based on their sensory properties, but also on the expected revenue once introduced in the market
- The determination of costs for toxicity testing needs to be done early in the selection process and reviewed constantly during the registration process

UPDATE FROM THE APPLICANTS

GENOTOXICITY TESTING



- Opportunity for feedback?
 - APDESK?
 - Correspondence with CEF Panel/Secretariat?
- Is *NEW* data always required?
 - What about substances with no structural alert?
 - What about substances for which closely related analogs have available data?
- In case of *in vitro* positives or less-than-conclusive results, there are several possible avenues that could be followed (Comet/MN, transgenic mutation, MN only, etc.) depending upon details/circumstances
 - **Further guidance/justification would be very helpful**

UPDATE FROM THE APPLICANTS

SUBMISSION FOR PRE-EVALUATION OF GENOTOXICITY DATA

Substance related data

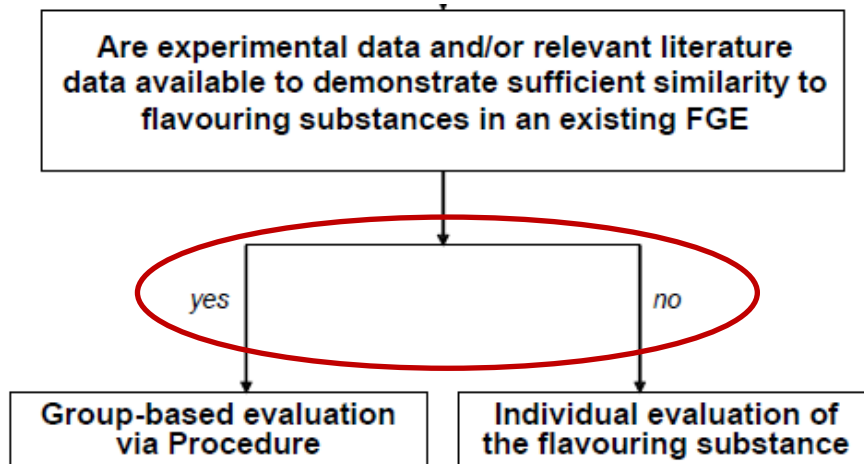
- Chemical name
- Structure
- CAS
- Analytical information (purity, etc.)
- Source material
- ...

Genotoxicity data

- Available genotox data and conclusion of the applicant :
 - Ames
 - *In vitro* Micronucleus
 - ...
- + study reports

UPDATE FROM THE APPLICANTS

GROUPING



- What is the process to agree on the "identification of structurally related substances"; does the applicant need to provide a justification for the selection?
- Confirmation from EFSA CEF panel needed, that there is sufficient structurally and/or metabolic similarity

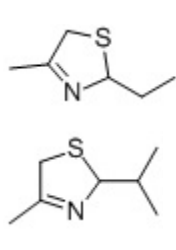
EFSA Feedback needed:

- ➔ to avoid unnecessary animal testing
- ➔ avoid unnecessary financial efforts

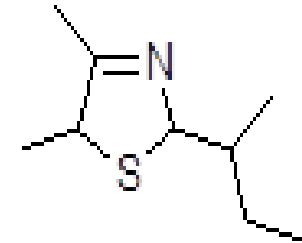
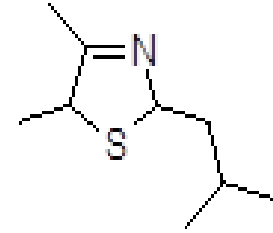
UPDATE FROM THE APPLICANTS

GROUPING/ APPLICANT EXAMPLES

- Group Approach: related to FGE 76 & FGE 21
- 2 New Notification Substances:



Read across to FL 15.032
and FL 15.029



❖ FL 15.032 = Footnote 10 material

- ✓ Ames Assay (*negative*)
- ✓ *In vitro* MN assay (*results equivocal*)
- ✓ Comet Assay (*negative*)

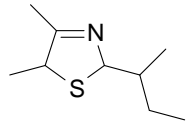
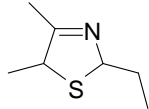
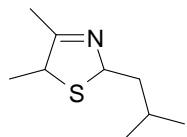
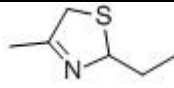
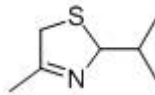
❖ FL 15.029

- ✓ 90-day NOEL = 1.2 mg/kg bw day

- APET new substance 1: 0.05 (normal) to 0.125 (max) mg/person/day
- APET new substance 2: 0.075 (normal) to 0.25 (max) mg/person/day

UPDATE FROM THE APPLICANTS

GROUPING OF STRUCTURALLY RELATED MATERIALS

Substance Name	FEMA No./ CAS No./EU FL No./JECFA No.	Structure
2-(2-butyl)-4,5-dimethyl-3-thiazoline ¹	3619 / 65894-82-8/ 15.029/1059	
2-Ethyl-4,5-dimethyl-3-thiazoline ¹	3620 / 76788-46-0/ 15.030/1058	
2-isobutyl-4,5-dimethyl-3-thiazoline ¹	3621 / 65894-83-9 / 15.032/ 1045	
2-ethyl-4-methyl-3-thiazoline	4695 / 41803-21-8 new candidate for EU UL/ 2114	
2-isopropyl-4-methyl-3-thiazoline	4767 / 67936-13-4 / new candidate for EU UL/2206	

¹ is under review by EFSA

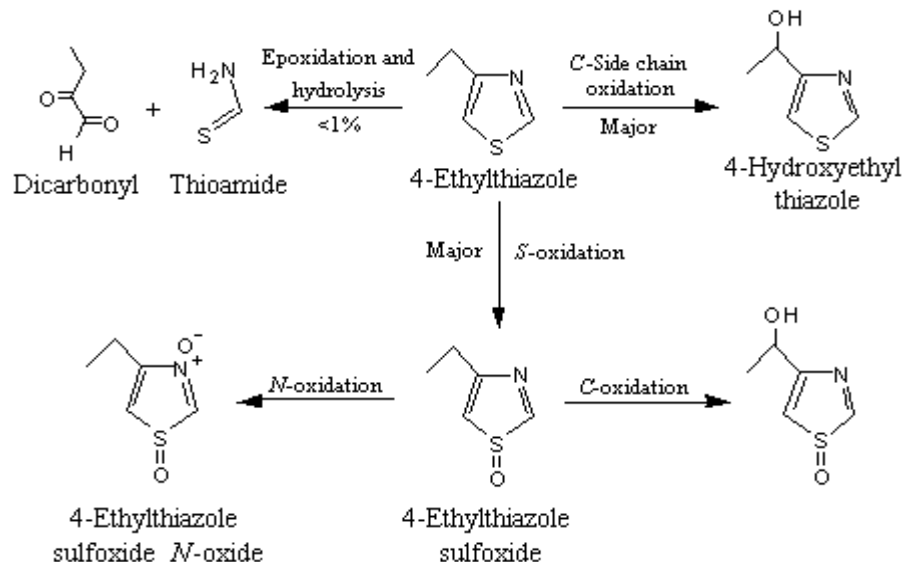
- The two new candidate substances are structurally similar to FGE 76 thiazolines and so are their flavour use levels.

UPDATE FROM THE APPLICANTS

GROUPING OF STRUCTURALLY RELATED MATERIALS

Support for Structural & Metabolic Similarity to Flavouring Substances in FGE 76 and FGE 21

- Experimental data: limited to thiazole, showing oxidation of the sulfur to form the corresponding sulfoxide and sulfone as the most favoured route.



- Literature data: both NNS have been evaluated by JECFA and expected to be metabolized similarly to already evaluated thiazolines.

<http://www.inchem.org/documents/jecfa/jecmono/v50je12.htm>

Derivatives of thiazoline in this group of flavouring substances are substituted in the 2-, 4- and 5-positions. Substances in this group are expected to be metabolized primarily by oxidation of the ring sulfur.

http://whqlibdoc.who.int/publications/2008/9789241660594_eng.pdf?ua=1 (page 252)

Thiazoline derivatives (Nos 1759–1762), being cyclic sulfides, are metabolized primarily by S-oxidation to yield corresponding sulfoxides and sulfones (Nelson & Cox, 2000).

UPDATE FROM THE APPLICANTS

GROUPING OF STRUCTURALLY RELATED MATERIALS

Support for Structural & Metabolic Similarity to Flavouring Substances in FGE 76 and FGE 21

[Literature data \(continued\)](#)

<http://www.efsa.europa.eu/en/efsajournal/pub/3451.htm>

FGE21, Rev4: It may be speculated that the substances in these groups are metabolised primarily by oxidation of the ring-S, or, if applicable, via N-oxidation. In addition, metabolism of the ring substituents is likely to occur.

<http://www.efsa.europa.eu/en/efsajournal/doc/3455.pdf>

FGE76, Rev1: For 18 of the remaining 21 substances the Panel agreed with the JECFA that they can not be expected to be metabolised to innocuous products. The 18 substances were allocated to one of the 10 structural subgroups identified in FGE.21Rev3. Taking these substances through the Procedure, it can be estimated that the intakes (MSDI) are below the thresholds for their structural classes II and III, and as the JECFA concluded that adequate NOAELs provides a sufficient safety margin, these substances were concluded at step B4 in the Procedure to be of no safety concern by the JECFA.

UPDATE FROM THE APPLICANTS

GROUPING OF STRUCTURALLY RELATED MATERIALS

EFSA feedback...

missing information. In particular, the justification provided by the applicant according to which the two new substances would be structurally related to the candidate substances in FGE.76 is not sufficiently supported. The applicant is requested to provide further detailed scientific justification for the read across approach. In the absence of robust justification, the limitations identified in our previous letter

- What data is required to provide scientific justification for using the group approach?
- What about *in silico* metabolic profiling?

UPDATE FROM THE APPLICANTS

INTAKE

- APET serves as a conservative “pre-market” estimate of intake for designating toxicity testing requirements (hazard testing)
 - Based on technically justified use levels from industry
 - Focused on high-end consumer of products
- Can other data be used to refine intake estimates prior to launching toxicity testing?
 - Intake estimates from other areas of the world
 - Use of probabilistic models
 - Benchmarking of use levels against materials of similar taste modality & potency
- Combined exposures Estimates
 - Data sources (including non-food): can EFSA give guidance as to which data sources should be consulted?
 - Grouping and co-use (reflecting market reality)

UPDATE FROM THE APPLICANTS

TOXICITY TESTING

- Opportunity to share preliminary experimental details/protocols as experiments are designed?
 - APDESK?
 - Correspondence with CEF Panel/Secretariat?
 - Is *NEW* data always required?
 - What about substances for which closely related analogs have available data?
- Experimental design can be challenging and often requires further follow-up/communication once dossier is submitted
 - Palatability issues
 - Material availability for very low exposure ingredients
 - Alpha-2u-globulin effects
 - Dietary stability/assessment of multi-component ingredients

UPDATE FROM THE APPLICANTS

COST RELATED ISSUES

■ Toxicity Studies

- 90-day toxicity study: 120000 EUR
- reprotoxicity/development screening assay: 70000 EUR

■ Genotoxicity Studies

- *In vitro* Ames assay: 3400 EUR
- *In vitro* Micronucleus (MNvit HML): 13500 EUR
- *In vivo* Micronucleus (rat bone marrow): 25000 EUR
- *In vivo* Comet assay: 30000 + 8500 EUR per additional tissue

- **Overall other administrative costs for dossier preparation** (excl. toxicity studies): Up to 125000 EUR per application (according to quotations from service providers)

UPDATE FROM THE APPLICANTS

FINAL REMARKS

The flavour industry is innovation driven and committed to do research and develop new flavourings. Therefore a consistent global approach, based on sound science, for the safety assessment of flavoring ingredients is of high relevance.

Over the last years industry has always shown its commitment to high safety standards in providing additional data to demonstrate the safety of materials already in the market.

This commitment also applies to new applications under CAP.

Offering the possibility to ask the panel for feedback upfront would be instrumental inasmuch applicants could:

- Learn if the genotoxicity tests are sufficient to clear the materials from concerns
- Run the tests deemed necessary by the panel
- Get confirmation if grouping of a new material is possible
- Avoid animal testing when not necessary

Thank You!

Questions?