Follow-up meeting on the web-based public consultation on the draft Aspartame of ANS/EFSA

Brussels, April 09th, 2013

French Agency for Food, Environment and Occupational Health & Safety (Anses)

Expertise methodology

Working group set up following the publication of the draft ANS EFSA opinion.

Experts from different fields: Toxicologists, Epidemiologist, Specialists in nutrition and metabolic diseases…

Examined items:

- **Chronic toxicity studies**
- **Toxicity led by APM metabolites**
- **Epidemiologic studies**
- **Reprotoxicity studies and relevance of the PKU model**

Risk characterization

- **Reprotoxicity studies showed NOAELs ranging from 1000 to 4000 mg/kg bw/d**
- **EFSA based the risk characterization on PKU data**
- **Anses questionned this approach for the following reasons.**

Phe toxicity

- **The proposed mode of action is a direct toxicity effect of Phe**
- **This MoA could be unsufficient to adress the teratogenic effects observed in animal studies :**
  - **The competition between Phe and other amino acids leading to a decrease of the Phe available to the fetus is not demonstrated**
  - **(lack of PK data increasing uncertainty)**

Aspartame metabolites (except Phe)

- **PKU model does not take into account APM metabolism**
- **Methanol is one metabolite of APM leading to the production of formaldehyde and of formate**
- **Excess of Phe leads to the excretion of phenyl-pyruvate, phenyl-acetate or phenyl-lactate**

- **The multiple substances appearing after administration of APM could interact with many cellular targets. PKU model does not take into account the interaction or synergistic effects of these molecules.**

Anses WG conclusions

- **The PKU model that adresses the direct Phe toxicity as the only mode of action presents some weaknesses.**
- **WG considers that additional toxicity mode of action (or synergistic effects) could explain teratogenic effects observed in animals.**

- **WG recommends to decrease uncertainties by collecting PK data of Phe and metabolites after APM oral administration.**

Anses WG recommendations

- **Due to uncertainties with regard to the modes of action, Anses WG recommends to the ANS panel to consider the revision of the current ADI :**
  - **Either in considering the NOAELs reported from the reprotoxicity studies**
    - **Or**
  - **In taking into account additional uncertainty factor**

Back-up