**Safety evaluation: hazard and risk**

**HAZARD**

The *potential* to cause an adverse effect: an inherent property of the molecule – which does not take-dose response into account.

**RISK**

The *likelihood* of that property being expressed – under relevant exposure conditions.

*All things are toxic and there is nothing without poisonous qualities: it is only the dose which makes something a poison.* *(Paracelsus 1493-1541)*
Chemical safety assessment

- The approaches used were developed internationally by the WHO-JECFA (Joint Expert Committee on Food Additives) – since about 1957
- Europe adopted and adapted – by SCF and EFSA – for additives, pesticides and contaminants
- Each chemical is assessed separately in a range of studies in which the dose is increased until some adverse effect (hazard) is produced
The risk assessment paradigm

1. HAZARD IDENTIFICATION
   - What can it do?

2. HAZARD CHARACTERISATION
   - What is the dose-response?
   - What would be a "safe" dose for humans?

3. INTAKE ASSESSMENT
   - What is the intake by humans?

4. RISK CHARACTERISATION
   - Is the human intake safe?

Hazard identification for food additives:

1. In vitro and animal studies
   - Genetic
     - Various genetic endpoints in bacteria and mammalian cells, screen for potential carcinogens
     - Usually single dose study
   - Acute
   - Short-term
     - Repeated daily dose for 14-28 days, identifies the target organ
   - Subchronic
     - Repeated daily doses for 90 days, gives dose-response, used for dose selection in chronic studies
   - Chronic
     - Repeated daily dose for two years in rodents, used to investigate carcinogenicity, usual source of NOAEL
   - Reproductive
     - Dosing occurs before, during and after reproduction to investigate effects on spermatogenesis, ovulation, fecundity, embryonic, fetal, and neonatal development
Role of human studies (2)

• The most relevant species
• Remove the need for uncertainty factors for interspecies extrapolation
• A means of investigating allergies and idiosyncratic intolerances not identified in animal studies
• “where human data of good quality are available these would take precedence over animal data”

Role of human studies (1)

• Usually limited to
• Metabolism and pharmacokinetics (ADME)
• Human tolerance
• Reversible pharmacological effects
• Epidemiological studies
• Nutritional effects (e.g. upper safe levels of vitamins and minerals)
Role of human studies (3):
Disadvantages and limitations

- For ethical reasons rarely address toxic endpoints directly (only tolerance) and some non-consensual groups (e.g. infants) and there should be potential benefits
- Intervention studies commonly of limited statistical power and duration (cf. animal studies)
- Many confounders in epidemiological studies on food and food ingredients
- “History of safe use” usually anecdotal and not supported by health records

<table>
<thead>
<tr>
<th>HAZARD CHARACTERISATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold effects</td>
</tr>
<tr>
<td>Analyse dose-response data to define most sensitive toxic effect – that produced the lowest doses in the most sensitive species</td>
</tr>
<tr>
<td>Define a daily intake that does NOT produce this effect</td>
</tr>
<tr>
<td>The acceptable daily intake (ADI) is determined by dividing the experimental no observed adverse effect levels (NOAELs) in the most sensitive animal studies (for long-term and short-term intake) by an uncertainty factor to give a margin of safety to allow for possible species differences and human variability (“not appreciable risk”)</td>
</tr>
</tbody>
</table>
**Dose-response in animals**

```
% Response

Dose (mg/kg/day)
```

**“Safe” intake for humans**

```
% Response

Dose (mg/kg/day)
```

Divide NOAEL by safety or uncertainty factor – usually 100

**The use of uncertainty or safety factors**

```
SPECIES DIFFERENCES         HUMAN VARIABILITY
```

```
10                     10
```

A 100-fold uncertainty or safety factor has been used by bodies such as WHO, SCF/EFSA, FDA, FSA and COT for the past 50 years to extrapolate from a group of test animals to the human population.
European Food Safety Authority

The European Food Safety Authority (EFSA) is the keystone of European Union (EU) risk assessment regarding food and feed safety. In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks.

European Food Safety Authority

Scientific Panel on Food Additives and Nutrient Sources Added to Foods (ANS)

Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA)
European Food Safety Authority

National authorities

Submission for Food Additive Evaluations
Safety Evaluation

New food additives or nutrients added to foods have to be evaluated by the EFSA ANS panel. Submissions for this evaluation have to follow the guidance on submission for food additive evaluations.
Safety Evaluation

PART I ADMINISTRATIVE DATA

PART II TECHNICAL DATA
1. Identity of substance
2. Microbiological characteristics
3. Proposed chemical and microbiological specifications
4. Manufacturing process
5. Methods of analysis in food
6. Reaction and fate in food
7. Case of need and proposed uses
8. Exposure
9. Additives produced by microbiological processes
10. Additives produced from genetically modified organisms
11. Information on national authorisations

PART III TOXICOLOGICAL DATA
1. General framework for the toxicological evaluation of food additives
2. Study protocols
3. Toxicological section of the dossier
   1. Core studies
   2. Other studies
4. Data reporting
5. Review of results and conclusions

PART IV REFERENCES AND REPORTS
1. List of references
2. Appended papers and study reports
Safety Evaluation

New food additives or nutrients added to foods have to be evaluated by the EFSA ANS panel. Submissions for this evaluation have to follow the guidance on submission for food additive evaluations.

Examples:

```
Scientific Opinion
The use of taurine and D-glucuronohydrate as constituents of the so-called “energy” drinks

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food
(Question No EFSA-Q-2007-113)

Adopted on 15 January 2009
```
Safety Evaluation

Examples:

Assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children’s behaviour

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC)

(Question No EFSA-Q-2007-171)

Adopted on 7 March 2008

Safety Evaluation

Examples:

SCIENTIFIC OPINION

Scientific Opinion on the re-evaluation Tartrazine (E 102)

EFSA Panel on Food Additives and Nutrition Sources added to Food (ANS)

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Additives and Nutrition Sources added to Food provides a scientific opinion re-evaluating the safety of Tartrazine (E 102). Tartrazine has been previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1989 and the JECFA Scientific Committee for Additives (SCAF) in 1977 and 1986. Both committees established a daily tolerable intake of 0.05 mg/kg body weight. The Panel was not provided with a new study from which the new ADI could derive and no new data were presented. The Panel concluded that the previous tolerable intake established by the JECFA committees in 1989 and 1986 has not been exceeded by Tartrazine, and that the tolerable intake established by the JECFA committees in 1989 and 1986 is confirmed. The Panel also concluded that the ADI for Tartrazine is conservative in children, with an intake in the lower quartile in the European diet. The Panel concluded that Tartrazine can still be used as a basis for setting the ADI, if necessary, and that the ADI for Tartrazine should be reviewed in the framework of the Evaluation of the ADIs. The Panel also concluded that the recommendations for a maximum level of 0.05 mg/kg weight should be maintained. The Panel concluded that the current tolerable intake of 0.05 mg/kg weight should be maintained. The Panel also concluded that the current tolerable intake of 0.05 mg/kg weight should be maintained. The Panel also concluded that the current tolerable intake of 0.05 mg/kg weight should be maintained.
Safety Evaluation

Examples:

SCIENTIFIC OPINION

L-selenomethionine as a source of selenium added for nutritional purposes to food supplements

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food


Adopted on 14 May 2009

EXPOSURE ASSESSMENT
Why nutrition surveys?

Evaluation of diet and nutrition (health aspects):
- Supply of energy and macronutrients
- Supply of micro nutrients (vitamins, minerals, trace elements)
- Supply of whole foods (e.g. fruit and vegetables)

Evaluation of food safety (safety and toxicological aspects):
- Exposure to nutrients, additives, contaminants

Evaluation of nutrition behaviour (sociological and psychological aspects):
- Differences in dietary behaviour in response to socioecononmical factors

Nutrition survey methodology

Direct methods
- Determination of nutrient requirement and nutritional status
  - static indicators
  - functional indicators

Indirect methods
- Determination of food (and nutrient) intake
  - retrospective
    - 24-hour recall
    - diet history
    - food frequency questionnaire
    - food budget
  - prospective
    - weighed food records
    - inventory method
    - estimated food record
    - etc

Indirect methods
- available data is evaluated, e.g. food balance sheets
Nutrition survey methodology

Nutrition surveys are intended to measure the ingested diet as accurately as possible without influencing the survey participants in their dietary behaviour.

With increasing period of the survey the more accuracy about dietary variation can be achieved while also the impact on the survey itself on the dietary behaviour increases.

There has been no golden standard identified so far.

Nutrition survey methodology

24-hour recall
- „What did you eat during the past 24 hours?”
- Determination of nutrient intake by food composition tables

pros:
- rapid and easy
- dietary habits are not influenced
- appropriate for large samples

cons:
- errors in estimating amounts
- deliberately false records

data from FAOSTAT data, FAO 2005
Nutrition survey methodology

Number of days required to classify 80% of the population into tertiles of nutritional intake with 95% confidence interval

<table>
<thead>
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<th>Nutrient</th>
<th>Range in days</th>
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<td>Energy</td>
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<tr>
<td>Total fat</td>
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<tr>
<td>Protein</td>
<td>5 – 7</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>2 – 4</td>
</tr>
<tr>
<td>Fibre</td>
<td>5 – 10</td>
</tr>
<tr>
<td>Iron</td>
<td>12 – 19</td>
</tr>
<tr>
<td>Calcium</td>
<td>3 – 5</td>
</tr>
</tbody>
</table>

JL Volatier, A Turrini and D Welten for the EFCOSUM Group.

Nutrition survey methodology

Food Frequency Questionnaires
- Assessment of diet quality
- Questionnaire is self-administered or interviewer follows a standardised questionnaire

Pros:
- Digital evaluation
- Large samples

Cons:
- False reporting
- Misunderstanding
- Low compliance if done via mail
Nutrition survey methodology

Food Frequency Questionnaires
- FFQs must be validated
- A compromise has to be found between effort of filling in the questionnaire and amount of information collected

Methods: Questionnaire Validation

A total of 51 individuals (26 female, 25 male) were asked to fill out the CAT and a 3 d weighing record (including all foods and beverages consumed, i.e. not focusing on caffeine itself).

7 consecutive saliva samples were collected from these subjects via a commercially available saliva collection system (Salivette) on day 2 and 3 of the recording period.
Results: Validation CAT

![Graph showing Caffeine exposure (mg/d) vs. 3-Tage Schätzprotokoll]

Caffeine exposure (mg/d)

Data comparability

Parameters having an impact on data comparability of different methodology in nutrition surveys:

- Size and structure of sample (e.g. age groups, total population, etc.);
- Time frame of survey;
- Methodological aspects (FFQ, 24 recall, weighed or estimated food records);
- Length of survey;
- Version of food composition table;
- Food categorisation system.

<table>
<thead>
<tr>
<th>Country</th>
<th>Type</th>
<th>N</th>
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<tbody>
<tr>
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<tr>
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<td>DK</td>
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<td>FI</td>
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<td>Dietary record</td>
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<td>UK</td>
<td>24 h</td>
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From foods to nutrients

- Translation into units of weight
- Translation from combined foods into basic foods
- Grouping of comparable foods
- Combination of basic foods with the food composition table
- Statistics
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Bezüge aus dem Fotobuch

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- Codex Alimentarius
- GSFA's food category system
- CIAA Food Categorizing System
- EFSA Concise European Food Consumption Database Classification System
- ...
From foods to nutrients

Exposure Assessment of Food Additives

- Budget method (tier 1): estimation of maximum theoretical exposure based on authorised use levels and maximum consumption of foods and beverages
- Estimation based on nutrition surveys and maximum permitted use levels of the consumed foods (tier 2).
- Estimation based on nutrition surveys and actual use levels (tier 3)
  - Estimates are provided for both average consumer (chronic exposure) as well as the “heavy consumer” (97.5. percentile, acute exposure) and the “heavy user” (97.5. percentile of users only).

From foods to nutrients

- Translation into units of weight
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- Statistics
Statistics

Statistical issues

Distribution of serum ferritin concentration in the New Zealand population from the 1997 National Nutrition Survey (n=3,369; unweighed)
Statistics

Average intake of alcoholic beverages of all adults (a) and average intake of alcoholic beverages of users (b) (those adults only consuming alcoholic beverages excluding those not consuming alcoholic beverages, in g/d, from 24h-Recalls)