

## SCIENTIFIC OPINION

### Statement on a conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010<sup>1</sup>

#### EFSA Panel on Food additives and Nutrient Sources added to Food (ANS)<sup>2,3</sup>

European Food Safety Authority (EFSA), Parma, Italy

#### ABSTRACT

The Panel on Food Additives and Nutrient Sources added to Food (ANS) provides a scientific statement presenting a conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010. This framework will be used in the evaluation made by the Panel, but the expert judgement of the scientific background, on a case-by-case basis, remains essential to reach a final conclusion. The outcome of the re-evaluation of food additives taking into account all available information is presented in the document, as well as the exposure assessment scenarios to be carried out by the Panel considering the use levels set in the legislation and the availability of adequate usage or analytical data.

© European Food Safety Authority, 2014

#### KEY WORDS

Commission Regulation (EU) No 257/2010, food additives, re-evaluation, risk assessment

<sup>1</sup> On request from EFSA, Question No EFSA-Q-2014-00194, adopted on 15<sup>th</sup> May 2014.

<sup>2</sup> Panel members: Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Pierre Galtier, David Gott, Ursula Gundert-Remy, Jürgen König, Claude Lambré, Jean-Charles Leblanc, Alicja Mortensen, Pasquale Mosesso, Rose Martin, Dominique Parent-Massin, Agneta Oskarsson, Ivan Stankovic, Paul Tobback, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright. Correspondence: [ftp@efsa.europa.eu](mailto:ftp@efsa.europa.eu)

<sup>3</sup> Acknowledgement: The Panel wishes to thank the members of the Working Group “A” Food Additives and Nutrient Sources: Pierre Galtier, Rainer Gürtler, Ursula Gundert-Remy, Claude Lambré, Jean-Charles Leblanc, Pasquale Mosesso, Dominique Parent-Massin, Ivan Stankovic, Christina Tlustos and Matthew Wright and of the Working Group “B” Food Additives and Nutrient Sources: Fernando Aguilar, Polly Boon, Riccardo Crebelli, Birgit Dusemund, David Gott, Torben Hallas-Møller, Jürgen König, Oliver Lindtner, Daniel Marzin, Inge Meyland, Alicja Mortensen, Agneta Oskarsson, Iona Pratt †, Paul Tobback, Ine Waalkens-Berendsen and Rudolf Antonius Woutersen for the preparatory work on this scientific opinion and EFSA staff: Paolo Colombo, Ana Rincon, Alexandra Tard and Stavroula Tasiopoulou for the support provided to this scientific opinion.

† Deceased.

Suggested citation: EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food), 2014. Statement on a conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010. EFSA Journal 2014;12(6):3697, 11 pp. doi:10.2903/j.efsa.2014.3697

Available online: [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal)

## SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Additives and Nutrient Sources added to Food (ANS) to provide a scientific statement on a conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010.

In the context of this re-evaluation, there are several scientific issues with the risk assessment of food additives of low intrinsic toxicity, e.g. substances with acceptable daily intake (ADI) “not specified” (no numerical ADI), food additives authorised in food categories according to *quantum satis* (QS) and food additives that whilst they are not of low intrinsic toxicity, are of low toxicological concern as used in food.

The purpose of this statement is to present a conceptual framework for the risk assessment of certain food additives defined as above, thus allowing the potential for abbreviated outputs of risk assessments. This framework will be used in the evaluation made by the Panel, but the expert judgement of the scientific background, on a case-by-case basis, remains essential to reach a final conclusion.

In the case of the re-evaluation of food additives, the ANS Panel is frequently confronted by a lack of usage and analytical data and ADME and toxicity data, and the latter, if available, often do not meet the quality criteria specified by current internationally recognised testing guidelines such as the OECD guidelines.

EFSA has issued one or more public calls for data on food additives to be re-evaluated. In many cases, these calls for data are unsuccessful, leaving the Panel in the position that the safety of the compound is assessed with limited and/or inadequate information on use (uses and use levels) and biological data.

Exposure assessment is an integral part of the risk assessment paradigm and its absence prevents the Panel from concluding on the safety of the food additive concerned. For those food additives for which no maximum permitted levels (MPLs) are set and which are authorised at QS, information on actual use levels is required. In the absence of reliable data, exposure cannot be estimated. The exposure assessment scenarios to be carried out by the Panel considering the use levels set in the legislation and the availability of adequate usage or analytical data are presented in this document.

The Panel has devised a conceptual framework outlining the outcome of the re-evaluation of food additives by the Panel, taking into account all available information.

## TABLE OF CONTENTS

Abstract .....	1
Summary .....	2
Table of contents .....	3
Background as provided by EFSA .....	4
Terms of reference as provided by EFSA .....	4
Evaluation.....	5
1. Introduction .....	5
2. Definitions .....	5
3. Specific considerations .....	6
4. Background for the proposed conceptual framework.....	6
4.1. Level of toxicity of a compound.....	6
4.2. Limited usage data .....	7
Conclusions .....	7
Appendix .....	9
Glossary and abbreviations .....	11

## BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No 1333/2008<sup>4</sup> of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under Commission Regulation (EU) No 257/2010<sup>5</sup>.

Priority criteria have been defined for the re-evaluation of the currently approved food additives taking into consideration the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive.

According to the programme for the re-evaluation of food additives, EFSA should request the necessary data in order to complete the re-evaluation of a food additive by an open call for data or by contacting the parties that submitted data on the food additive. In many cases, these EFSA calls for data were unsuccessful, leaving the EFSA Panel of Food Additives and Nutrient Sources added to Food (ANS) in the position where the risk has to be assessed with inadequate information on use (uses and use levels) and biological data are very limited and, if available, they are often out-dated.

In this context, in order to increase the transparency of the re-evaluations made by the EFSA ANS Panel and to ensure a consistent approach for certain food additives falling under the re-evaluation programme of Commission Regulation (EU) No 257/2010, EFSA proposes to share the conceptual framework for determining the outcome of the risk assessment of food additives on the basis of available data, thus allowing the potential for abbreviated outputs of risk assessments.

## TERMS OF REFERENCE AS PROVIDED BY EFSA

In accordance with Article 29(1) of Regulation (EC) No 178/2002<sup>6</sup>, the European Food Safety Authority asks its scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) to provide a scientific statement on a conceptual framework for the risk assessment of food additives re-evaluated under Commission Regulation (EU) No 257/2010.

In particular this will elaborate possible outcomes on the risk assessment within the re-evaluation programme for certain food additives which are predominately used as *quantum satis* uses or which were previously evaluated as of low intrinsic toxicity (acceptable daily intake not specified) or of low toxicological concern as used in food.

---

<sup>4</sup> Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008.

<sup>5</sup> Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010.

<sup>6</sup> Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 31.2.2002.

## EVALUATION

### 1. Introduction

A programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under Regulation (EU) No 257/2010<sup>5</sup>.

In the context of this re-evaluation, there are several scientific issues with the risk assessment of food additives<sup>7</sup>:

- which are of low intrinsic toxicity, e.g. substances with acceptable daily intake (ADI) “not specified” (no numerical ADI),
- which are authorised in food categories according to *quantum satis* (QS) (Regulation (EC) No 1333/2008<sup>4</sup>) which precludes a reliable exposure estimate,
- which, whilst they are not of low intrinsic toxicity, are of low toxicological concern as used in food, e.g. sodium hydroxide.

The purpose of this statement is to present a conceptual framework for the risk assessment of certain food additives defined as above, thus allowing the potential for abbreviated outputs of risk assessments. This framework will be used in the evaluation made by the Panel, but the expert judgement of the scientific background, on a case-by-case basis, remains essential to reach a final conclusion.

### 2. Definitions

Both the EU Scientific Committee for Food (SCF)<sup>8</sup> and the Joint FAO/WHO Expert Committee on Food Additives (JECFA)<sup>9</sup> gave a definition of ADI “not specified”. The two definitions are very close and the SCF definition is: “*ADI not specified is a term used when, on the basis of the available toxicological, biochemical and clinical data, the total daily intake of the substance, arising from its natural occurrence and/or its present use or uses in food at the levels necessary to achieve the desired technological effect, will not represent a hazard to health*<sup>10</sup>. For this reason, the establishment of a numerical limit for the ADI is not considered necessary for these substances. Any additive allocated as “ADI not specified” must be used according to good manufacturing practice, i.e. it should be technological efficacious, should be used at the lowest level necessary to achieve its technological effect, should not conceal inferior quality or adulteration, and should not create a nutritional imbalance”.

The Panel on Food Additives and Nutrient Sources added to Food (ANS) noted that this definition of ADI “not specified” includes the requirement that the total dietary exposure arising from the use of the food additive at the levels necessary to achieve the desired effect and from natural occurrence in food does not represent a risk (expressed by the SCF as hazard to health). It is therefore not possible to re-evaluate food additives with an ADI “not specified” without adequate information on reported or analytical level of food additive uses. If this information is not available, it is not possible to perform a dietary exposure assessment and therefore having a risk characterisation conclusion for the safety of the food additive and to conclude for the ANS Panel that the uses and use levels of the food additive are safe for the general population. Therefore, in this case the Panel considered that this definition of an ADI “not specified” is no longer fit for purpose.

<sup>7</sup> In particular food additives belonging to Groups I and II in Annex II of Regulation (EC) No 1333/2008.

<sup>8</sup> Report of the Scientific Committee for Food. Twenty-fifth series. First series of food additives of various technological functions. Opinion expressed on 18 May 1990.

Available online: [http://ec.europa.eu/food/fs/sc/scf/reports/scf\\_reports\\_25.pdf](http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_25.pdf)

<sup>9</sup> JECFA definition on ADI “not specified”: Glossary of terms. Available online: <http://www.who.int/foodsafety/chem/jecfa/glossary.pdf>

<sup>10</sup> The Panel interpreted the term “hazard to health” as risk.

The Panel further noted that in the definition of ADI “not specified”, JECFA<sup>9</sup> indicated that the compound must be of very low toxicity. “Very low toxicity” was, however, not defined and requires scientific judgement; the Panel considered that it was therefore important to specify the criteria that will be applied to establish that a food additive is of “very low toxicity”. For such compounds, the Panel uses the term of “low intrinsic toxicity”.

*Quantum satis* (QS) is defined in the Regulation (EC) No 1333/2008<sup>4</sup> on food additives and means that no maximum numerical level is specified and substances shall be used in accordance with good manufacturing practice, at a level not higher than is necessary to achieve the intended purpose and provided the consumer is not misled.

### 3. Specific considerations

In the case of the re-evaluation of food additives, the ANS Panel is frequently confronted by a lack of usage and analytical data and ADME and toxicity data, and the latter, if available, often do not meet the quality criteria specified by current internationally recognised testing guidelines such as the OECD guidelines.

In the framework of the re-evaluation programme, EFSA has issued one or more public calls for data on all food additives to be re-evaluated.

In many cases, these calls for data are unsuccessful, leaving the Panel in the position that the safety of the compound is assessed with limited and/or inadequate information on use (uses and use levels) and biological data.

As exposure assessment is an integral part of the risk assessment paradigm (hazard identification, hazard characterisation, exposure assessment and risk characterisation), its absence prevents the Panel from concluding on the safety of the food additive concerned. Current practice, in the absence of reported usage data and when maximum permitted levels (MPLs) have been established, is to initially consider the MPL for each food category even though the food additive may be used at a lower level than the MPL. For those food additives for which no MPLs are set and which are authorised according to QS, information on actual use levels or observed analytical data is needed. In the absence of reliable data, the Panel considered that the exposure cannot be estimated.

Accordingly, the Panel has devised a conceptual framework approach for the re-evaluation of food additives (Appendix, Figure 1) outlining the outcome of the safety assessment depending on the type of data (exposure and biological) available. The exposure assessment scenarios to be carried out by the Panel considering the use levels set in the legislation, (“regulatory maximum level exposure assessment” scenario) and the availability of adequate usage or analytical data (“refined exposure assessment” scenario), are shown in the Appendix, Figures 2 and 3, respectively.

## 4. Background for the proposed conceptual framework

### 4.1. Level of toxicity of a compound

In determining whether a compound is of low intrinsic toxicity, the Panel will consider the following elements:

- The food additive and/or its breakdown products/metabolites is/are identical to a compound that is a normal constituent of the body or of the regular diet and its uses would not contribute significantly to the internal levels<sup>11</sup> or the dietary exposure,
- A lack of concern with respect to genotoxicity, preferably assessed using data from studies with the compound or potentially from read across from relevant related compounds,

<sup>11</sup> To be discussed case-by-case but generally within the normal range of variation.

- There is no indication of systemic and local adverse effects in relevant toxicological studies,
- Relevant toxicokinetic information (“negligible” absorption, no accumulation (bio persistence)),
- Absence of structural alerts by considering structure activity relationships,
- No indication of adverse effects (including toxicological and pharmacological) in humans from other possible uses of the compound (e.g. pharmaceutical) at doses similar or, preferably higher than those used as a food additive and of adequate duration and route of exposure,
- No indication for the presence of toxicologically relevant impurities/residuals.

#### 4.2. Limited usage data

In the absence of MPLs for a food additive and if usage or analytical data received from interested parties refer only to a small proportion of the food categories in which the food additive is authorised, the safety assessment carried out by the Panel will be limited to these uses and use levels.

### CONCLUSIONS

The outcome of the re-evaluation of food additives by the Panel, taking into account all available information will be (Appendix, Figure 1):

- A. In the absence of reliable information on both exposure and toxicity, the conclusion will be: Not possible to assess the safety due to the absence of data<sup>12</sup>.
- B. If the exposure can be adequately assessed but if there is no reliable information on toxicity the conclusion will depend on whether the compound is, or is not, identical to an endogenous compound<sup>13</sup>:
  - If the food additive and/or its breakdown products/metabolites is/are not identical to an endogenous compound, the conclusion will be: Not possible to conclude on the safety due to the lack of adequate hazard characterization.
  - If the food additive and/or its breakdown products/metabolites is/are identical to a compound which is a normal constituent in the body (an endogenous compound) and/or is a regular component of the diet, the conclusion will be based on the comparison between naturally occurring exposure and the exposure arising from the uses of the food additive.
- C. In the absence of reliable information on exposure from its use as a food additive, the conclusion will depend on the outcome of the hazard identification/characterisation:
  - If the toxicity database is adequate and only show adverse effects as a consequence of an overload of the physiological processes of the test species, the conclusion will be: Low probability of adverse health effects in humans at doses that do not induce nutritional imbalance in animals (no need for a numerical ADI). In that case, the proposal of an indicative total exposure might be considered by the Panel.
  - If the toxicity database is adequate and shows some adverse effects, the conclusion will be: Allocate an ADI, additional data on exposure are required to conclude on the safety of uses and use levels.

<sup>12</sup> A long history of use without reported adverse effects is not considered strong supporting evidence.

<sup>13</sup> The Panel will also consider the other criteria characterising a substance with a low intrinsic toxicity.

- If the toxicity database is inadequate, the conclusion will be: Not possible to assess the safety due to the absence of data.
- D. If there is reliable information for both exposure and toxicity, the conclusion will depend on the hazard identification/characterisation:
- If there is no hazard, the conclusion will be: No safety concern at the reported uses and use levels, no need for a numerical ADI.
  - If an effect was reported: a numerical ADI is derived from the lowest point of departure (NOAEL, BMD) and the ADI will be compared with the daily exposure:
    - ❖ If the calculated daily dietary exposure is below the ADI, the conclusion will be: No safety concern at the reported uses and use levels.
    - ❖ If the calculated daily dietary exposure is above the ADI, the conclusion will be: Not possible to conclude that the current uses and use levels are safe.

APPENDIX

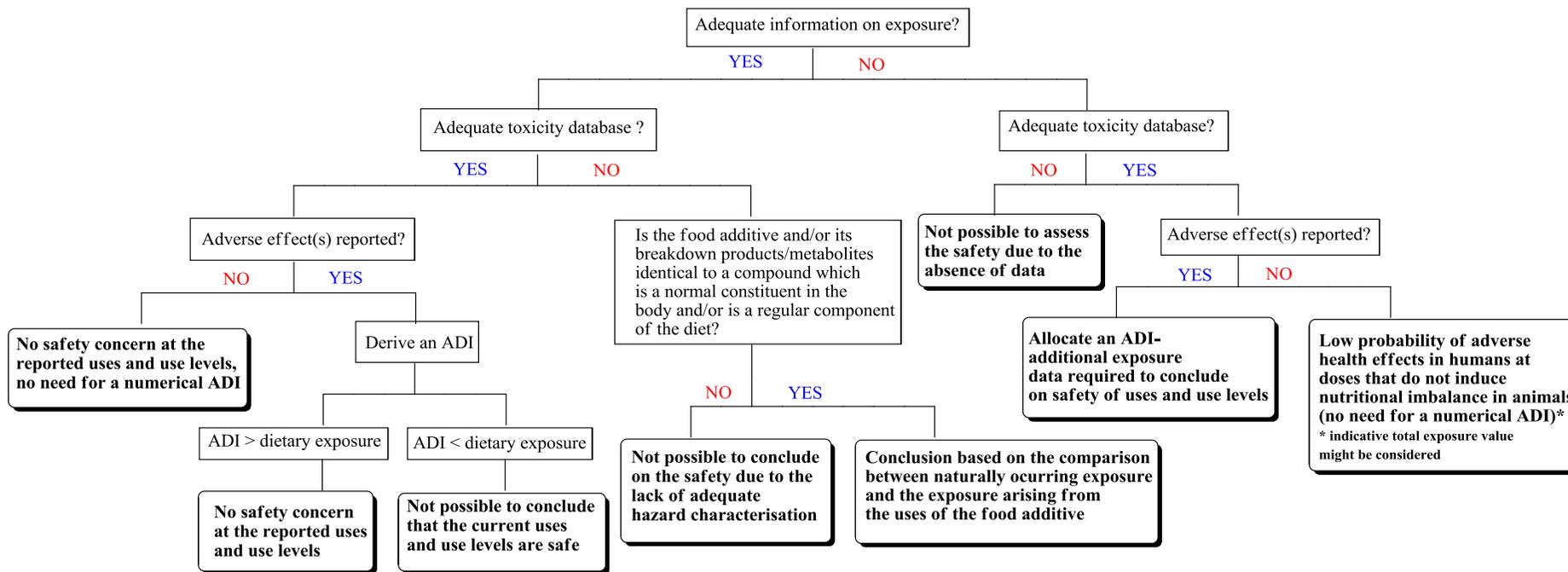
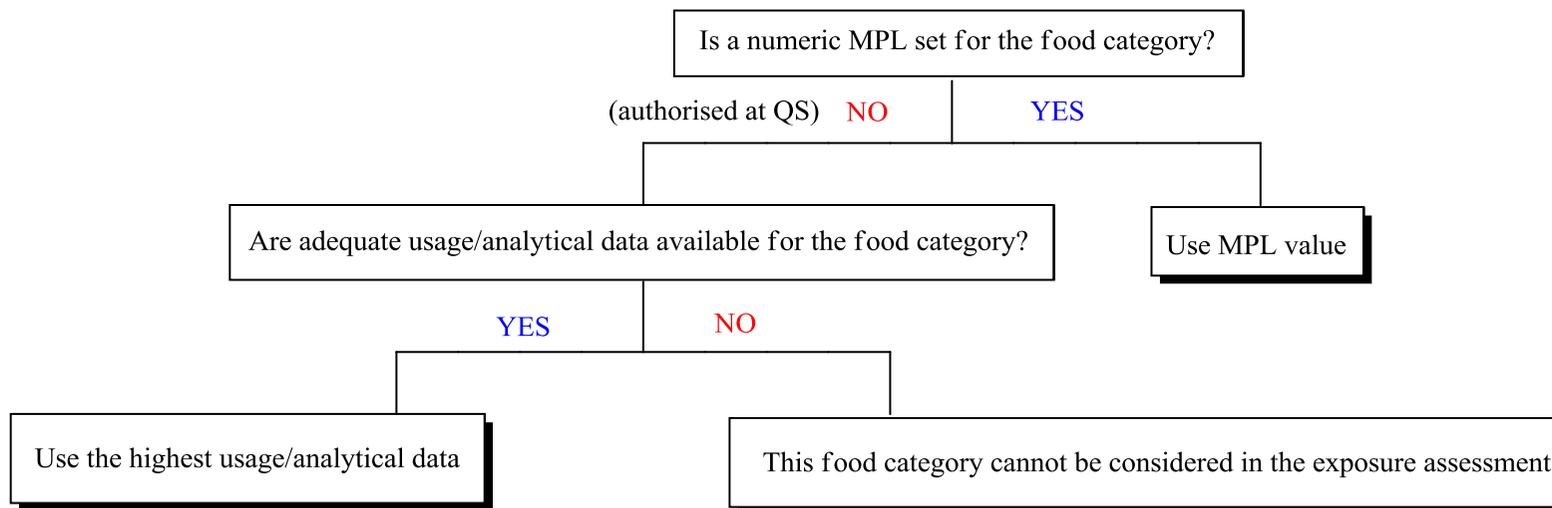
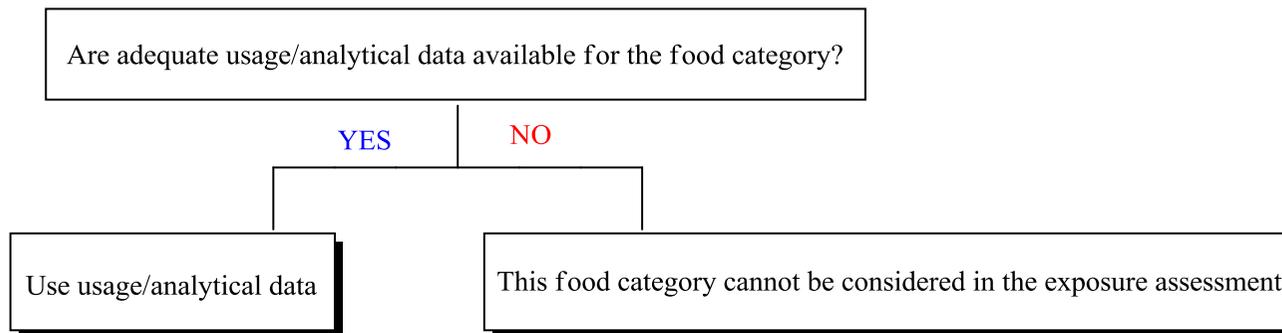


Figure 1: The conceptual framework approach for the re-evaluation of certain food additives



**Figure 2:** “Regulatory Maximum Level Exposure Assessment” scenario



**Figure 3:** “Refined Exposure Assessment” scenario

**GLOSSARY AND ABBREVIATIONS**

ADI	Acceptable daily intake
ADME	Absorption, distribution, metabolism and excretion
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
BMD	Benchmark dose
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MPL	Maximum permitted level
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
QS	<i>Quantum satis</i>
SCF	EU Scientific Committee on Food