EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 308 (FGE.308): Glucose Pentaacetate and Sucrose Octaacetate

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 308 (FGE.308):

Glucose Pentaacetate and Sucrose Octaacetate[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to evaluate two flavouring substances in the Flavouring Group Evaluation 308, using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These two flavouring substances belong to chemical group 30 Annex I of the Commission Regulation (EC) No 1565/2000.

The candidate substances are glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-16.081].

The candidate substances [FL-no: 09.258 and 16.081] possess four and nine chiral centres, respectively. The stereoisomeric compositions have been specified for both substances..

The candidate substances belong to structural class II.

None of the substances have been reported to occur naturally in foods.

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1 On request from the Commission, Question No EFSA-Q-2010-01504 and EFSA-Q-2010-01505, adopted on 4 February 2011.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Groups on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Wilfried Bursch, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Gerard Pascal, Iona Pratt, Gerrit Speijers, Harriet Wallin and EFSA's staff member Kim Rygaard Nielsen for the preparatory work on this scientific Opinion.

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In its evaluation, the Panel as a default used the "Maximised Survey-derived Daily Intake" (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe. However, when the Panel examined the information provided by the European Flavouring Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach.

In the absence of more precise information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a "modified Theoretical Added Maximum Daily Intake" (mTAMDI) approach based on the normal use levels reported by Industry. In those cases where the mTAMDI approach indicated that the intake of a flavouring substance might exceed its corresponding threshold of concern, the Panel decided not to carry out a formal safety assessment using the Procedure. In these cases the Panel requires more precise data on use and use levels.

The estimated daily *per capita* intake of the two candidate substances are 0.061 microgram [FL-no: 09.258] and 210 microgram [FL-no: 16.081]. These are below the threshold of concern for structural class II.

It is concluded that the genotoxicity data available do not preclude the evaluation of these substances through the Procedure.

The metabolism data available were sufficient to conclude that the candidate substances are rapidly absorbed, metabolised to innocuous products and excreted through normal biological mechanisms.

A 90-day study is available on the candidate substance glucose pentaacetate [FL-no: 09.258] which is considered to be supporting for both substances in subgroup two.

The estimated intake for each of the two candidate substances [FL-no: 09.258 and 16.081] in structural class II, based on the mTAMDI, is 230000 and 2700 microgram/person/day, respectively, which is above the threshold of concern of 540 microgram/person/day. Thus, for the candidate substances [FL-no: 09.258 and 16.081] further information is required. This would include more reliable intake data and then, if required, additional toxicological data.

In order to determine whether the conclusion for the candidate substances which have been evaluated using the Procedure can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity for the materials of commerce have been provided for the two flavouring substances evaluated through the Procedure.

Thus, the two substances glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-no: 16.081] would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

KEYWORDS

Food safety, flavouring, acetate, pentaacetate, octaacetate.

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996a) lays down a Procedure for the establishment of a list of flavouring substances the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2009/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

After the completion of the evaluation programme the Union List of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96) (EC, 1996a).

TERMS OF REFERENCE

The European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances in the Register prior to their authorisation and inclusion in a Union List according to Commission Regulation (EC) No 1565/2000 (EC, 2000a). In addition, the Commission requested EFSA to evaluate newly notified flavouring substances, where possible, before finalising the evaluation programme.

In addition, in letter of 17 May 2010 the Commission requested EFSA to carry out a risk assessment on glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-16.081] in accordance with Commission Regulation (EC) No 1565/2000:

"The European Commission requests the European Food Safety Authority to carry out a safety assessment on glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-16.081], in accordance with Commission Regulation (EC) No 1565/2000 by end 2010".

The deadline of the Terms of Reference was negotiated to 30 May 2011.

ASSESSMENT

1. Presentation of the Substances in Flavouring Group Evaluation 308

1.1. Description

The present revision of Flavouring Group Evaluation 308 (FGE.308), using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000 (the Procedure – shown in schematic form in Annex I of this FGE), deals with two flavouring substances (candidate substances) from chemical group 30 of Annex I of Commission Regulation (EC) No 1565/2000 (EC, 2000a).

The candidate substances under consideration in the present evaluation, with their chemical Register names, FLAVIS- (FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufacturers Association- (FEMA-) numbers, and structures are listed in Table 1.

No supporting substances have been identified for this group.

The outcome of the safety evaluation is summarised in Table 2a.

1.2. Stereoisomers

It is recognised that geometrical and optical isomers of substances may have different properties. Their flavour may be different, they may have different chemical properties resulting in possible variability in their absorption, distribution, metabolism, elimination and toxicity. Thus, information must be provided on the configuration of the flavouring substance, i.e. whether it is one of the geometrical/optical isomers, or a defined mixture of stereoisomers. The available specifications of purity will be considered in order to determine whether the safety evaluation carried out for candidate substances for which stereoisomers may exist can be applied to the material of commerce. Flavouring substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number etc.).

The two candidate substances [FL-no: 09.258 and 16.081] possess four and nine chiral centres, respectively. The stereoisomeric compositions have been specified for both substances (Flavour Industry, 2010e) (see Table 1).

1.3. Natural Occurrence in Food

The two candidate substances are not reported to occur naturally in any food items (TNO, 2010).

2. Specifications

Purity criteria for the substances have been provided by the Flavour Industry (Flavour Industry, 2010e) (Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000a), this information is adequate for both candidate substances (see Section 1.2 and Table 1).

3. Intake Data

Annual production volumes of the flavouring substances as surveyed by the Industry can be used to calculate the "Maximised Survey-derived Daily Intake" (MSDI) by assuming that the production figure only represents 60 % of the use in food due to underreporting and that 10 % of the total EU population are consumers (SCF, 1999a).

However, the Panel noted that due to year-to-year variability in production volumes, to uncertainties in the underreporting correction factor and to uncertainties in the percentage of consumers, the reliability of intake estimates on the basis of the MSDI approach is difficult to assess.

The Panel also noted that in contrast to the generally low *per capita* intake figures estimated on the basis of this MSDI approach, in some cases the regular consumption of products flavoured at use levels reported by the Flavour Industry in the submissions would result in much higher intakes. In such cases, the human exposure thresholds below which exposures are not considered to present a safety concern might be exceeded.

Considering that the MSDI model may underestimate the intake of flavouring substances by certain groups of consumers, the SCF recommended also taking into account the results of other intake assessments (SCF, 1999a).

One of the alternatives is the "Theoretical Added Maximum Daily Intake" (TAMDI) approach, which is calculated on the basis of standard portions and upper use levels (SCF, 1995) for flavourable beverages and foods in general, with exceptional levels for particular foods. This method is regarded

as a conservative estimate of the actual intake by most consumers because it is based on the assumption that the consumer regularly eats and drinks several food products containing the same flavouring substance at the upper use level.

One option to modify the TAMDI approach is to base the calculation on normal rather than upper use levels of the flavouring substances. This modified approach is less conservative (e.g., it may underestimate the intake of consumers being loyal to products flavoured at the maximum use levels reported) (EC, 2000a). However, it is considered as a suitable tool to screen and prioritise the flavouring substances according to the need for refined intake data (EFSA, 2004a).

3.1. Estimated Daily *per Capita* Intake (MSDI Approach)

The intake estimation is based on the Maximised Survey-derived Daily Intake (MSDI) approach, which involves the acquisition of data on the amounts used in food as flavourings (SCF, 1999a). These data are derived from surveys on annual production volumes in Europe. These surveys were conducted in 1995 by the International Organization of the Flavour Industry, in which flavour manufacturers reported the total amount of each flavouring substance incorporated into food sold in the EU during the previous year (IOFI, 1995). The intake approach does not consider the possible natural occurrence in food.

Average *per capita* intake (MSDI) is estimated on the assumption that the amount added to food is consumed by 10 % of the population[4] (Eurostat, 1998). This is derived for candidate substances from estimates of annual volume of production provided by Industry and incorporates a correction factor of 0.6 to allow for incomplete reporting (60 %) in the Industry surveys (SCF, 1999a).

The total annual volume of production of the two candidate substances in the present Flavouring Group Evaluation (FGE.308) from use as flavouring substances in Europe has been reported to be approximately 1000 (Flavour Industry, 2010e).

On the basis of the annual volumes of production reported for the two candidate substances, the daily *per capita* intakes for each of these flavourings have been estimated. The estimated daily *per capita* intake of glucose pentaacetate [FL-no: 09.258] is 0.061 microgram and that of sucrose octaacetate [FL-no: 16.081] is 210 microgram (Table 2).

3.2. Intake Estimated on the Basis of the Modified TAMDI (mTAMDI)

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995).

The assumption is that a person may consume a certain amount of flavourable foods and beverages per day.

For the candidate substances information on food categories and normal and maximum use levels[5,6] were submitted by the Flavour Industry (Flavour Industry, 2010e).

The two candidate substances are used in flavoured food products divided into the food categories, outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000a), as shown in

[4] EU figure 375 millions. This figure relates to EU population at the time for which production data are available, and is consistent (comparable) with evaluations conducted prior to the enlargement of the EU. No production data are available for the enlarged EU.

[5] "Normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i).

[6] The normal and maximum use levels in different food categories (EC, 2000) have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

Table 3.1. For the present calculation of mTAMDI, the reported normal use levels were used. In the case where different use levels were reported for different food categories the highest reported normal use level was used.

Table 3.1 Use of Two of Three Candidate Substances

Food category	Description	Flavourings used
01.0	Dairy products, excluding products of category 2	None
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Only [FL-no: 16.081]
03.0	Edible ices, including sherbet and sorbet	Only [FL-no: 16.081]
04.1	Processed fruits	None
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	None
05.0	Confectionery	Only [FL-no: 16.081]
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	None
07.0	Bakery wares	Only [FL-no: 16.081]
08.0	Meat and meat products, including poultry and game	Only [FL-no: 09.258]
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	None
10.0	Eggs and egg products	None
11.0	Sweeteners, including honey	None
12.0	Salts, spices, soups, sauces, salads, protein products etc.	None
13.0	Foodstuffs intended for particular nutritional uses	None
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	Both
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	Only [FL-no: 16.081]
15.0	Ready-to-eat savouries	None
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	None

According to the Flavour Industry the normal use levels for the two candidate substances are in the range of 5.18 - 5.46 mg/kg food for [FL-no: 16.081] and 100 - 1500 mg/kg food for [FL-no: 09.258], and the maximum use levels are in the range of 8.72-9.92 mg/kg food for [FL-no: 16.081] and 100 - 1500 mg/kg food for [FL-no: 09.258] (Flavour Industry, 2010e) (see Table II.1.2, Annex II).

The mTAMDI value is respectively 230000 and 2700 microgram/person/day for the candidate substances [FL-no: 09.258] and [FL-no: 16.081] from structural class II (see Section 5).

For detailed information on use levels and intake estimations based on the mTAMDI approach, see Section 6 and Annex II.

4. Absorption, Distribution, Metabolism and Elimination

For the two candidate substances, data on the absorption and metabolism of one of the candidate substances glucose pentaacetate [FL-no: 09.258] have been submitted (Domingues et al., 1960).

Using ^{14}C labels in both the glucose and acetate moieties, it was found that β-D-glucose pentaacetate is rapidly absorbed, metabolised and excreted primarily as expired carbon dioxide.

Partial hydrolysis of β-D-glucose pentaacetate occurs with the more highly acetylated molecules being excreted in the urine more quickly than the lower acetylated molecules.

It is anticipated that sucrose octaacetate would be metabolised in a similar way as glucose pentaacetate.

It can be anticipated that the candidate substances are metabolised to innocuous products and rapidly excreted.

For more detailed information, see Annex III.

5. Application of the Procedure for the Safety Evaluation of Flavouring Substances

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach. Where the mTAMDI approach indicates that the intake of a flavouring substance might exceed its corresponding threshold of concern, a formal safety assessment is not carried out using the Procedure. In these cases the Panel requires more precise data on use and use levels. For comparison of the intake estimations based on the MSDI approach and the mTAMDI approach, see Section 6.

For the safety evaluation of the candidate substances from chemical group 30 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the substances are summarised in Table 2.

Step 1

The two candidate substances glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-16.081] are classified according to the decision tree approach by Cramer et al. (Cramer et al., 1978) into structural class II.

Step 2

Step 2 requires consideration of the metabolism of the candidate substances. It can be anticipated that glucose pentaacetate [FL-no: 09.258] and sucrose octaactetate [FL-16.081] are metabolised to innocuous products. Accordingly, the evaluation of these candidate substances proceeds via the A-side of the Procedure scheme.

Step A3

The two candidate substances glucose pentaacetate [FL-no: 09.258] and sucrose octaactetate [FL-16.081] have estimated European daily *per capita* intakes of 0.061 and 210 microgram, respectively (Table 2). These intakes are below the threshold of concern of 540 microgram/person/day for structural class II.

Based on results of the safety evaluation sequence of the Procedure, these two candidate substances, proceeding via the A-side of the Procedure scheme, do not pose a safety concern when used as flavouring substances at the estimated levels of intake, based on the MSDI approach.

6. Comparison of the Intake Estimations Based on the MSDI Approach and the mTAMDI Approach

The estimated intake for each of the two candidate substances [FL-no: 09.258 and 16.081] in structural class II, based on the mTAMDI, is 230000 and 2700 microgram/person/day, respectively, which is above the threshold of concern of 540 microgram/person/day.

Thus, for the candidate substances [FL-no: 09.258 and 16.081] further information is required. This would include more reliable intake data and then, if required, additional toxicological data.

For comparison of the MSDI and mTAMDI values, see Table 6.1.

Table 6.1 Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
09.258	Glucose pentaacetate	0.061	230000	Class II	540
16.081	Sucrose octaacetate	210	2700	Class II	540

7. Considerations of Combined Intakes from Use as Flavouring Substances

Because of structural similarities of candidate and supporting substances, it can be anticipated that many of the flavourings are metabolised through the same metabolic pathways and that the metabolites may affect the same target organs. Further, in case of combined exposure to structurally related flavourings, the pathways could be overloaded. Therefore, combined intake should be considered. As flavourings not included in this FGE may also be metabolised through the same pathways, the combined intake estimates presented here are only preliminary. Currently, the combined intake estimates are only based on MSDI exposure estimates, although it is recognised that this may lead to underestimation of exposure. After completion of all FGEs, this issue should be readdressed.

The total estimated combined daily *per capita* intake of structurally related flavourings is estimated by summing the MSDI for individual substances.

On the basis of the reported annual production volumes in Europe (EFFA, 2008c; Flavour Industry, 2010e), the combined estimated daily *per capita* intake as flavourings of the two candidate substances belonging to structural class II is approximately 210 microgram. This value does not exceed the threshold of concern for structural class II of 540 microgram/person/day.

8. Toxicity

8.1. Acute Toxicity

Data are available for one of the candidate substances, sucrose octaactetate [FL-no: 16.081]. The oral LD_{50} value in mice is 1600 mg/kg body weight (bw).

The acute toxicity data are summarised in Annex IV, Table IV.1.

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

Subacute and subchronic toxicity data are available for one of the candidate substances (glucose pentaacetate [FL-no: 09.258]).

A 90-days study has been carried out using dietary levels of β-D glucose pentaacetate of 0 %, 1 %, 5 % and 10 % in the diet, equivalent to 1, 5 and 10 g/kg body weight (bw)/day. Comparison with control animals revealed no differences between the groups, except a significant increase in lung weights was observed in all male test groups, although this did not appear to be dose related. Subsequent to this study, a group of 4 animals were maintained for 2 years from the high dose group with no adverse effects observed, although this was not carried out in accordance with guidelines for a 2 year carcinogenicity study (Zeitlin et al., 1960).

A further search in open literature did not provide any further relevant information.

Repeated dose toxicity data are summarised in Annex IV, Table IV.2.

8.3. Developmental / Reproductive Toxicity Studies

No data on developmental toxicity and reproductive toxicity have been identified for any of the candidate substances.

8.4. Genotoxicity Studies

In vitro data are only available for one candidate substance, sucrose octaactetate [FL-no: 16.081] with an Ames test, an UDS assay and a Mouse lymphoma forward mutation assay all giving negative results (Heck et al., 1989). Overall, the limited data available do not preclude their evaluation through the Procedure.

A further search in open literature did not provide any further relevant information.

Genotoxicity data are summarised in Annex IV, Table IV.4.

9. Conclusions

The two candidate substances are compounds containing acetate moieties from chemical group 30.

The two candidate substances glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-16.081] possess four and nine chiral centres, respectively. The stereoisomeric compositions have been specified for both substances. The two candidate substances belong to structural class II [FL-no: 09.258 and 16.081].

None of the substances have been reported to occur naturally in foods.

The estimated daily *per capita* intake of glucose pentaacetate [FL-no: 09.258] is 0.061 microgram and that of sucrose octaacetate [FL-no: 16.081] is 210 microgram. These are below the threshold of concern for structural class II.

It is concluded that the genotoxicity data available do not preclude the evaluation of these substances through the Procedure.

The metabolism data available were sufficient to conclude that the candidate substances are rapidly absorbed, metabolised to innocuous products and excreted through normal biological mechanisms.

A 90-day study is available on the candidate substance glucose pentaacetate [FL-no: 09.258] which is considered to be supporting for both substances.

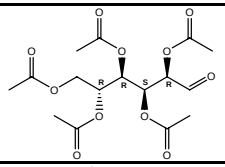
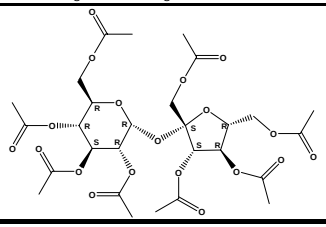
The estimated intake for each of the two candidate substances [FL-no: 09.258 and 16.081] in structural class II, based on the mTAMDI, is 230000 and 2700 microgram/person/day, respectively, which is above the threshold of concern of 540 microgram/person/day. Thus, for the candidate substances further information is required. This would include more reliable intake data and then, if required, additional toxicological data.

In order to determine whether the conclusion for the candidate substances which have been evaluated using the Procedure can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity for the materials of commerce have been provided for the two flavouring substances evaluated through the Procedure.

Thus, the two substances glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-no: 16.081] would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 308

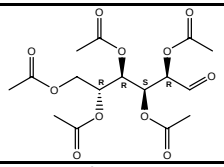
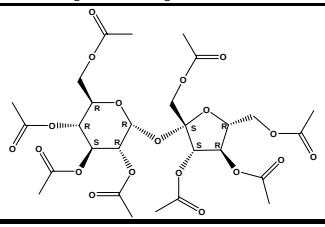
Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 308

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.258	Glucose pentaacetate		2524 3891-59-6	Solid $C_{16}H_{22}O_{11}$ 390.34	Practically insoluble Sparingly soluble	 110-115 NMR MS 95 %	n.a. n.a.	The CASrn referes to the D-Glucose pentaacetate. Industry informs that the 95 % assay minimum covers the complete acetylated D-glucose (D-glucose pentaacetate).
16.081	Sucrose octaacetate		3038 11819 126-14-7	Solid $C_{28}H_{38}O_{19}$ 678.60	Slightly soluble Freely soluble	260 82-89 NMR 95 %	n.a. n.a.	Industry informs that the 95 % assay minimum covers the complete acetylated alpha-D-glucopyranoside.

1) *Solubility in water, if not otherwise stated.*
2) *Solubility in 95 % ethanol, if not otherwise stated.*
3) *At 1013.25 hPa, if not otherwise stated.*
4) *At 20°C, if not otherwise stated.*
5) *At 25°C, if not otherwise stated.*

TABLE 2: SUMMARY OF SAFETY EVALUATION APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH)

Table 2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.258	Glucose pentaacetate		0.061	Class II A3: Intake below threshold	4)	6)	
16.081	Sucrose octaacetate		210	Class II A3: Intake below threshold	4)	6)	

1) *EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.*

2) *Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day , Class III = 90 µg/person/day.*

3) *Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.*

4) *No safety concern based on intake calculated by the MSDI approach of the named compound.*

5) *Data must be available on the substance or closely related substances to perform a safety evaluation.*

6) *No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).*

7) *Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.*

8) *No conclusion can be drawn due to lack of information on the purity of the material of commerce.*

ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), named the "Procedure", is shown in schematic form in Figure I.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999a), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b).

The Procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II, III) for which thresholds of concern (human exposure thresholds) have been specified. Exposures below these thresholds are not considered to present a safety concern.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1800, 540 or 90 microgram/person/day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996a).

In Step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- can the flavourings be predicted to be metabolised to innocuous products[7] (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous[8] (Step A4)?
- does a NOAEL exist on the flavourings or on structurally related substances (Step A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure.

The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

[7] *"Innocuous metabolic products": Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent" (JECFA, 1997a).*

[8] *"Endogenous substances": Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997a).*

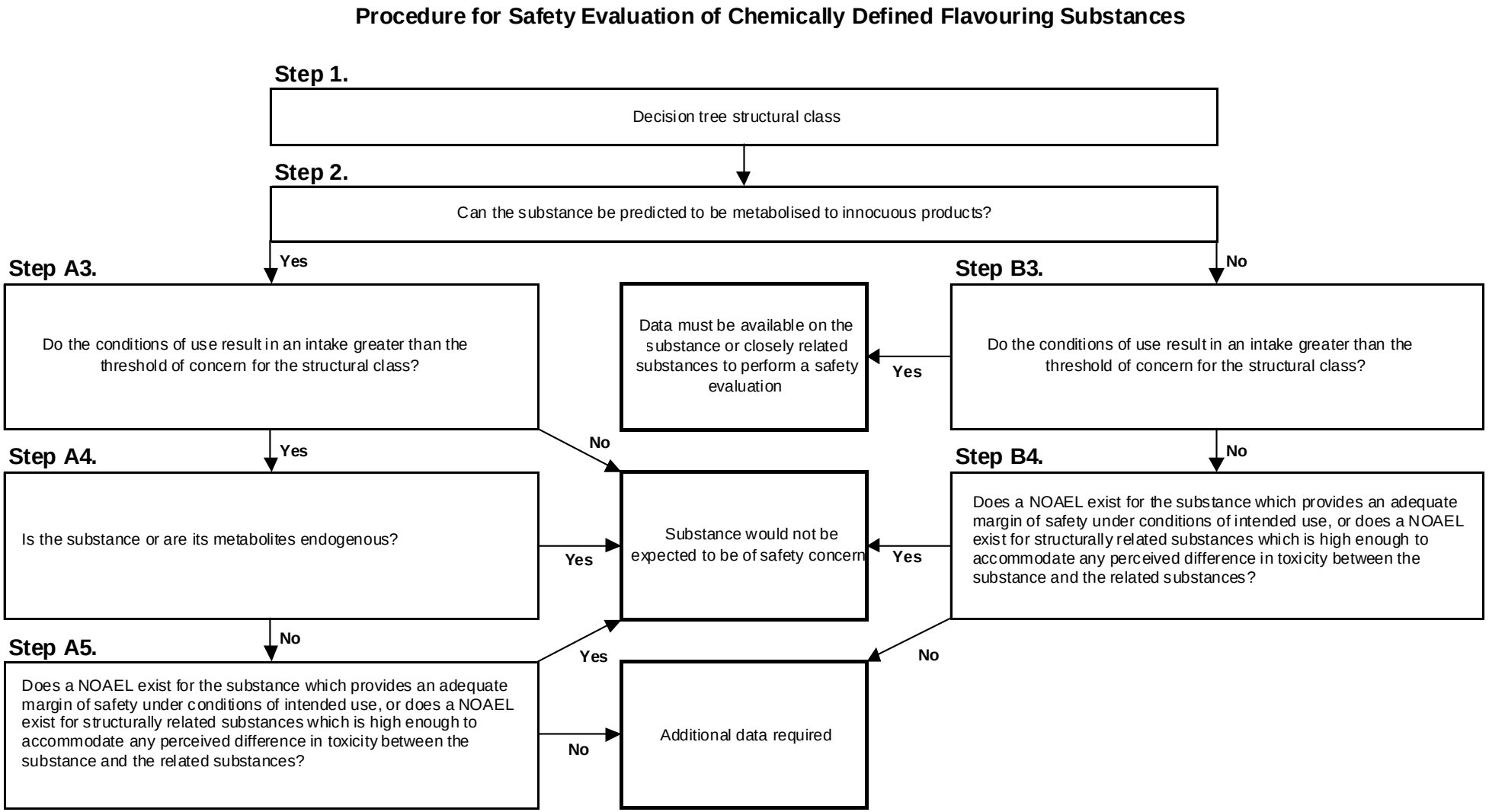


Figure I.1 *Procedure for Safety Evaluation of Chemically Defined Flavouring Substances*

ANNEX II: USE LEVELS / MTAMDI

II.1 Normal and Maximum Use Levels

For each of the 18 Food categories (Table II.1.1) in which the candidate substances are used, Flavour Industry reports a "normal use level" and a "maximum use level" (EC, 2000a). According to the Industry the "normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

Table II.1.1 Food categories according to Commission Regulation (EC) No 1565/2000 (EC, 2000a)

Food category	Description
01.0	Dairy products, excluding products of category 02.0
02.0	Fats and oils, and fat emulsions (type water-in-oil)
03.0	Edible ices, including sherbet and sorbet
04.1	Processed fruit
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds
05.0	Confectionery
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery
07.0	Bakery wares
08.0	Meat and meat products, including poultry and game
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms
10.0	Eggs and egg products
11.0	Sweeteners, including honey
12.0	Salts, spices, soups, sauces, salads, protein products, etc.
13.0	Foodstuffs intended for particular nutritional uses
14.1	Non-alcoholic ("soft") beverages, excl. dairy products
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts
15.0	Ready-to-eat savouries
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0

The "normal and maximum use levels" are provided by Industry for the two candidate substances in the present flavouring group (Table II.1.2).

Table II.1.2.Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.308 (Flavour Industry, 2010e).

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
09.258	-	-	-	-	-	-	-	-	1500	-	-	-	-	-	100	-	-	-
	-	-	-	-	-	-	-	-	1500	-	-	-	-	-	100	-	-	-
16.081	-	5,46	5,4	-	-	5,4	-	5,46	-	-	-	-	-	-	5,18	5,18	-	-
	-	8,77	8,77	-	-	8,72	-	8,77	-	-	-	-	-	-	9,92	9,92	-	-

II.2 mTAMDI Calculations

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amount of flavourable foods and beverages listed in Table II.2.1. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

Table II.2.1 Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995)

Class of product category	Intake estimate (g/day)
Beverages (non-alcoholic)	324.0
Foods	133.4
Exception a: Candy, confectionery	27.0
Exception b: Condiments, seasonings	20.0
Exception c: Alcoholic beverages	20.0
Exception d: Soups, savouries	20.0
Exception e: Others, e.g. chewing gum	e.g. 2.0 (chewing gum)

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 (EC, 2000a) and reported by the Flavour Industry in the following way (see Table II.2.2):

- Beverages (SCF, 1995) correspond to food category 14.1 (EC, 2000a)
- Foods (SCF, 1995) correspond to the food categories 1, 2, 3, 4.1, 4.2, 6, 7, 8, 9, 10, 13, and/or 16 (EC, 2000a)
- Exception a (SCF, 1995) corresponds to food category 5 and 11 (EC, 2000a)
- Exception b (SCF, 1995) corresponds to food category 15 (EC, 2000a)
- Exception c (SCF, 1995) corresponds to food category 14.2 (EC, 2000a)
- Exception d (SCF, 1995) corresponds to food category 12 (EC, 2000a)
- Exception e (SCF, 1995) corresponds to others, e.g. chewing gum.

Table II.2.2 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995)

	Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories		
Key	Food category	Food	Beverages	Exceptions
01.0	Dairy products, excluding products of category 02.0	Food		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03.0	Edible ices, including sherbet and sorbet	Food		
04.1	Processed fruit	Food		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Food		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07.0	Bakery wares	Food		
08.0	Meat and meat products, including poultry and game	Food		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10.0	Eggs and egg products	Food		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Food		
14.1	Non-alcoholic ("soft") beverages, excl. dairy products		Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts			Exception c
15.0	Ready-to-eat savouries			Exception b
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be	Food		

Table II.2.2 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995)

Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories
placed in categories 01.0 - 15.0	

The mTAMDI values (see Table II.2.3) are presented for the two flavouring substances in the present flavouring group, for which Industry has provided use and use levels (Flavour Industry, 2010e). The mTAMDI values are only given for the highest reported normal use levels.

TableII.2.3 Estimated intakes based on the mTAMDI approach

FL-no	EU Register name	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
09.258	Glucose pentaacetate	230000	Class II	540
16.081	Sucrose octaacetate	2700	Class II	540

ANNEX III: METABOLISM

III.1. Introduction

The present FGE consists of two candidate substances glucose pentaacetate [FL-no: 09.258] and sucrose octaacetate [FL-no: 16.081].

III.2. Absorption, Distribution and Elimination

For the candidate substances data are available on glucose pentaacetate [FL-no: 09.258]. Using ^{14}C labels in both the glucose and acetate moieties, it was found that β-D-glucose pentaacetate is rapidly absorbed, metabolised and excreted primarily as expired carbon dioxide (Domingues et al., 1960).

Absorption of glucose pentaacetate was almost complete within 4 hours. Absorption measured using glucose and acetate concentrations showed that the molecule is being partially hydrolysed in the GI tract and then the acetate moiety is rapidly absorbed.

Partial hydrolysis of β-D-glucose pentaacetate occurs with the more highly acetylated molecules being excreted in the urine more quickly than the lower acetylated molecules (Domingues et al., 1960). After 48 hours only 2 % of the radioactivity was measured in the faeces of the animals.

Of the acetate labelled molecule, 80 % of the radioactive label was excreted as expired carbon dioxide up to 48 hours after dosing and peaking at around 4 hours after dosing, whereas for the glucose labelled molecule, these figures were 65 % and one hour. These differences suggest that the molecule is only partially hydrolysed in the GI tract. Urinalysis of the rats fed the glucose labelled molecule showed that 11 % of the radiolabel was excreted in the urine compared to 4 % for the acetate labelled molecule.

It is anticipated that sucrose octaacetate would be absorbed, distributed and eliminated in a similar way to glucose pentaacetate.

A study was carried out using two similar substances, sucrose acetate isobutyrate and sucrose octaisobutyrate in rats, dogs, monkeys and humans (Reynolds, 1998). In humans, the majority (41-66 %) of the orally administered dose of ^{14}C sucrose acetate isobutyrate was eliminated as carbon dioxide within 11 days of dosing with the maximal rate of elimination occurring between 9 and 16 hours after dosing. Urinary elimination was rapid and accounted for 14-21 % of the dose and around 10 % of the dose was recovered in the faeces. The authors of this paper conclude that sucrose acetate isobutyrate is extensively metabolised in the GI tract probably to sucrose and partially acetylated sucrose and eliminated rapidly.

III.3. Metabolism

There are little data on the metabolism of the candidate substances.

Partial hydrolysis of β-D-glucose pentaacetate to acetate and various acetylated glucose derivatives occurs in the GI tract. Using chromatography of the urine, it was determined that as time progressed, the concentration of higher acetylated glucose derivatives decreased and the concentration of lower acetylated derivatives increased, suggesting that over time, continual deacetylation occurs (Domingues et al., 1960).

It is anticipated that sucrose octaacetate would be metabolised in a similar way as glucose pentaacetate.

Acetate is a normal metabolite in the body and is converted to acetyl CoA and enters the citric acid cycle (Stryer, 1988).

III.4. Summary and Conclusions

It can be anticipated that the two candidate substances are metabolised to innocuous products and rapidly excreted primarily in the expired air with lower concentrations in the urine and lower still in the faeces.

ANNEX IV: TOXICITY

Oral acute toxicity data are available for one candidate substance of the present Flavouring Group Evaluation from chemical group 30.

TABLE IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD_{50} (mg/kg bw)	Reference	Comments
Sucrose octaacetate [16.081]	Mice	NR	NR	1600	(Schafer & Bowles, 1985)	

NR: Not reported

Subacute / Subchronic / Chronic / Carcinogenic toxicity data are available for one candidate substance of the present Flavouring Group Evaluation from chemical group 30.

TABLE IV.2: SUBACUTE / SUBCHRONIC / CHRONIC / CARCINOGENICITY STUDIES

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
Glucose pentaacetate [09.258]	Rats; M, F 10	Oral	0, 1, 5, 10 g/kg bw/day	90 days	10	(Zeitlin et al., 1960)	Subsequent to this study, a group of 4 animals were maintained for 2 years from the high dose group with no adverse effects observed, although this was not carried out in accordance with guidelines for a 2 year carcinogenicity study.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental or reproductive toxicity data are available for the candidate substances of the present Flavouring Group Evaluation from chemical group 30.

In vitro mutagenicity/genotoxicity data are available for one candidate substance of the present Flavouring Group Evaluation from chemical group 30.

TABLE IV.4: GENOTOXICITY (*IN VITRO*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
Sucrose octaactetate [16.081]	Ames assay	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Up to 10000 microg/plate	Negative[1]	(Heck et al., 1989)	Published non-GLP study. No information concerning a possible cytotoxic effect nor on the number of concentrations tested. The test guidelines do not require more than 5 mg/plate. Due to the lack of some important details of study design and results the validity of the study cannot be evaluated.
	Unscheduled DNA synthesis	Rat primary hepatocytes	509 microg/ml	Negative	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Mouse lymphoma assay	L5178Y *tk* +/- mouse lymphoma cells	2000 microg/ml	Negative[1]	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.

[1] With and without S9.

GENOTOXICITY (*IN VIVO*)

No *In vivo* mutagenicity/genotoxicity data are available for the candidate substances of the present Flavouring Group Evaluation from chemical group 30.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
BW	Body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids Chemical Abstract Service
CHO	Chinese hamster ovary (cells)
CoA	Co Enzyme A
CoE	Council of Europe
DNA	Deoxyribonucleic acid
EC	European Commission
EFFA	European Flavour and Fragrance Association
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GI	Gastro Intestinal
ID	Identity
IOFI	International Organization of the Flavour Industry
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal Dose, 50%; Median lethal dose
MS	Mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
No	Number
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Program
SCE	Sister Chromatid Exchange
SCF	Scientific Committee on Food
SMART	Somatic Mutation and Recombination Test
TAMDI	Theoretical Added Maximum Daily Intake

UDS	Unscheduled DNA Synthesis
WHO	World Health Organisation