EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2014. Scientific Opinion on Flavouring Group Evaluation 91, Re vision 2 (FGE.91Rev2): Consid eration of simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA (53rd and 68th meetings) structurally related to aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in FGE.08Rev5 (2012).

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 91, Revision 2 (FGE.91Rev2): Consideration of simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA (53rd and 68th meetings) structurally related to aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in FGE.08Rev5 (2012)[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. The present consideration concerns a group of 44 simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 53rd and the 68th meeting. The substances were evaluated through a stepwise approach that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. For 36 substances considered in this FGE the Panel concluded that they would pose "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach For seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] the Panel decided, contrary to the JECFA that these substances could not be evaluated due to absence of a NOAEL from either one of these substances or from a structurally related substance. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been considered and for all 44 substances, the information is adequate. For candidate substance 3-(methylthio)heptenal [FL-no: 12.273], which contains 5 to7 % of an α,β-unsaturated aldehyde, 2-(E)-heptenal, with a possible genotoxic potential, the Panel cannot conclude that the material of commerce for this candidate substance is not of safety concern, until either this component is cleared with respect to a concern for genotoxicity, or this component is removed from the commercial product.

[1] On request from the European Commission, Question No EFSA-Q-2013-00412 to EFSA-Q-2013-00418, adopted on 21 May 2014.

[2] Panel members: Ulla Beckman Sundh, Mona-Lise Binderup, Claudia Bolognesi, Leon Brimer, Laurence Castle, Alessandro Di Domenico, Karl-Heinz Engel, Roland Franz, Nathalie Gontard, Rainer Gürtler, Trine Husøy, Klaus-Dieter Jany, Martine Kolf-Clauw, Wim Mennes, Maria Rosaria Milana, Iona Pratt †, Kettil Svensson, Maria de Fátima Tavares Poças, Fidel Toldra and Detlef Wölfle. Correspondence: fip@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Flavourings: Ulla Beckman Sundh, Leon Brimer, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, Wim Mennes, Gerard Mulder and Harriet Wallin for the preparatory work on this scientific opinion and the hearing experts: Vibe Beltoft, Pia Lund and Karin Nørby and EFSA staff: Annamaria Rossi and Kim Rygaard Nielsen for the support provided to this scientific opinion.

† Deceased

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KEY WORDS

sulfides, sulphides, thiols, JECFA 68th meeting, JECFA 53rd meeting, food safety, FGE.91

SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was asked to deliver a 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 CEF Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The previous version of this consideration dealt with 47 simple aliphatic and aromatic sulphides and thiols, which are in the Register and which were evaluated by the JECFA at its 53rd and 68th meetings. Since the previous evaluation, data have become available that alleviate a concern for genotoxicity, which was identified in the previous version of this FGE for seven tertiary thiols. These seven substances can now be evaluated through the procedure. In addition, three substances are no longer supported by Industry. This revision of FGE.91 therefore deals with 44 substances.

The Panel concluded that all the 44 substances in the JECFA flavouring groups of simple aliphatic and aromatic sulphides and thiols are structurally related to the aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in the Flavouring Group Evaluation 08, Revision 5 (FGE.08Rev5). The 44 JECFA evaluated substances are distributed into six subgroups of structurally related substances. The subgrouping corresponds to the subgrouping in FGE.08Rev5.

This revision is made because additional genotoxicity data have become available for 4-mercapto-4-methyl-2-pentanone [FL-no: 12.169] from FGE.74Rev3, which is a representative for the group of tertiary monothiols and therefore covers the seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] in this FGE. In addition, data on production volume and specification were submitted.

Although the available data are limited the Panel considered that for the 44 substances in FGE.91Rev2 the genotoxicity data do not preclude evaluating these substances through the Procedure.

However, the Panel noted that candidate substance 3-(methylthio)heptenal [FL-no: 12.273] contains 5 to 7 % of an α,β -unsaturated aldehyde, (2-(E)-heptenal [FL-no: 05.150], for which a concern has been raised due to the presence of a structural alert for genotoxicity. This substance is a candidate flavouring substance which is under evaluation in FGE.200Rev1 (FGE.19 subgroup 1.1.1).

The Panel agrees with the JECFA that all substances can be evaluated through the Procedure. For 34 substances the conclusion was that they do not pose a safety concern when used as flavouring substance at their estimated intake based on the MSDI approach.

For 10 substances [FL-no: 12.038, 12.077, 12.085, 12.108, 12.137, 12.138, 12.145, 12.162, 12.252 and 12.259] the Panel did not agree with the application of the Procedure by the JECFA for the following reasons:

For the substances [FL-no: 12.077, 12.108 and 12.162], the JECFA has cleared by the JECFA at step B5 (the MSDI < 1.5 μg person per day). However, the Panel considers that adequate NOAELs exist to evaluate these substances and concluded at step B4 “No safety concern at the estimated levels of intake based on the MSDI approach”.

For the tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259], contrary to the JECFA, the Panel concluded that there are no adequate NOAELs for these candidate substances

or from structurally related substances and that additional toxicity data are required to finalise the evaluation of these seven substances.

For 34 substances, use levels have been provided by the Industry. The mTAMDI figures for five substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural classes. For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For 10 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267 and 17.036] for which use levels have not been provided, use levels are needed to calculate the mTAMDI values in order to identify those flavouring substances that need a more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 44 JECFA evaluated substances, for which the Panel concluded that they could be evaluated through the Procedure, can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria and identity are available for all 44 substances.

Thus, for seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] evaluated through the Procedure, the Panel concluded that additional toxicity data are required.

For candidate substance 3-(methylthio)heptenal [FL-no: 12.273], which contains 5 to7 % of an α,β-unsaturated aldehyde, 2-(E)-heptenal, with a possible genotoxic potential, the Panel cannot conclude that the material of commerce for this candidate substance is not of safety concern, until either this component is cleared with respect to a concern for genotoxicity, or this component is removed from the commercial product.

For 36 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, 12.264, 12.265, 12.26712.274, 12.275, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297, 15.049 and 17.036] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.”.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of flavourings is regulated under Regulation (EC) No 1334/2008 of the European Parliament and Council of 16 December 2008[4] on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of Article 9(a) of this Regulation, an evaluation and approval are required for flavouring substances.

The Union list of flavourings and source materials was established by Commission Implementing Regulation (EC) No 872/2012[5]. The list contains flavouring substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000[6].

EFSA has considered the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluation of 47 simple aliphatic and aromatic sulphides and thiols and tertiary thiols evaluated in the flavouring group evaluation 91 (FGE.91) and its latest revision. The opinion was adopted on 24 November 2011. EFSA concluded in its opinion, contrary to the JECFA, that the seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] should not be evaluated using the Procedure due to concern for genotoxicity and, therefore, additional data was requested.

Information on the representative material, 2-methyl-4-oxopentane-2-thiol [FL-no: 12.169] from FGE.74 was submitted by the European Flavour Association and forwarded by the Commission to EFSA on 26 April 2013. This information is intended to cover as well the re-evaluation of the following seven tertiary thiols from FGE.91:

- 8-mercapto-p-menthan-3-one [FL-no: 12.038]
- p-menth-1-ene-8-thiol [FL-no: 12.085]
- 3-mercapto-3-methylbutan-1-ol [FL-no: 12.137]
- 3-mercapto-3-methylbutyl formate [FL-no: 12.138]
- 4-methoxy-2-methylbutane-2-thiol [FL-no: 12.145]
- 4-mercapto-4-methyl-2-pentanol [FL-no: 12.252]
- 1-mercapto-p-menthan-3-one [FL-no: 12.259]

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requests the European Food Safety Authority (EFSA) to evaluate this new information and, depending on the outcome, proceed to the full evaluation on these flavouring substances in accordance with Commission Regulation (EC) N° 1565/2000.

[4] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34-50.

[5] Commission implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p, 1-161.

[6] Commission Regulation No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96. OJ L 180, 19.7.2000, p. 8-16.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000, hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996; JECFA, 1997; JECFA, 1999a), hereafter named the "JECFA Procedure". The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance.

Intake

In its evaluation, the Panel as a default uses the Maximised Survey-derived Daily Intake (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe.

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour 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. It is noted that the JECFA, at its 65th meeting considered "how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods" (JECFA, 2006).

In the absence of more accurate 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.

As information on use levels for the flavouring substances has not been requested by the JECFA or has not otherwise been provided to the Panel, it is not possible to estimate the daily intakes using the mTAMDI approach for the substances evaluated by the JECFA. The Panel will need information on use levels in order to finalise the evaluation.

Threshold of 1.5 Microgram/Person/Day (Step B5) Used by the JECFA

The JECFA uses the threshold of concern of 1.5 microgram (µg)/person/day as part of the evaluation procedure:

"The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the

Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 µg per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 µg per day?")" (JECFA, 1999a).

In line with the Opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 µg per person per day.

Genotoxicity

As reflected in the Opinion of SCF (SCF, 1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *in vitro,* will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

In the consideration of the JECFA evaluated substances, the Panel will examine the structural relationship and metabolism features of the substances within the flavouring group and compare this with the corresponding FGE.

1. History of the Evaluation of the Substances in the Present FGE

The EFSA consideration in FGE.91 dealt with 45 substances, forty simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 68th meeting, 2007 and five tertiary thiols evaluated by JECFA at the 53rd meeting, 1999. For seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] adequate genotoxicity data were needed before the substances can be evaluated through the Procedure.

The first revision of FGE.91, FGE.91Rev1, included the assessment of two additional substances, benzyl methyl sulphide [FL-no: 12.077] and methyl phenyl sulfide [FL-no: 12.162]. These substances were evaluated by the JECFA at the 53rd meeting in 1999. Furthermore, additional information had been submitted on stereoisomerism for [FL-no: 12.108, 12.264, 12.267, 12.273, 12.274, 12.284, 12.285, 12.286, 12.287, 12.289, 12.290, 12.292, 12.297 and 15.049], on specifications for [FL no: 12.038, 12.253, 12.256, 12.274, 12.276, 12.284 and 12.297] and on composition of mixture for [FL-no: 12.153, 12.254, 12.256, 12.259] (EFFA, 2010; EFFA, 2011b).

Since the publication of FGE.91Rev1, three of the 47 candidate substances are no longer supported by the Industry for use as flavouring substances in Europe (DG SANCO, 2013a). The three substances are diethyl trisulfide [FL-no: 12.114], ethyl propyl trisulfide [FL-no: 12.256] and propyl propanethiosulfonate [FL-no: 12.272] and they will therefore not be considered any further.

FGE	Opinion adopted	Link	No. of substances
FGE.91	24 September 2009	http://www.efsa.europa.eu/en/efsajournal/pub/1337.htm	45
FGE.91Rev1	23 November 2011	http://www.efsa.europa.eu/en/efsajournal/pub/2459.htm	47
FGE.91Rev2			44

The present revision of FGE.91, FGE.91Rev2 concerns the re-consideration of seven JECFA-evaluated substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] considered in FGE.91 where the Panel concluded that the Procedure should not be applied until adequate genotoxicity data would be available.

For 2-methyl-4-oxopentane-2-thiol [FL-no: 12.169] a bacterial reverse mutation assay has been provided (Mc Garry, 2012). This substance [FL-no: 12.169] from FGE.74Rev3 is considered a representative for tertiary monothiols in the Union List, i.e. [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] in the present FGE, [FL-no: 12.241] in FGE.74Rev3 and [FL-no: 12.304] in FGE.08Rev5.

Since the publication of FGE.91Rev1 tonnage figures for seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] and additional information on specification for eight substances [FL-no: 12.085, 12.145, 12.162, 12.252, 12.259, 12.274, 12.284 and 15.049] have been provided by Industry (IOFI, 2012; EFFA, 2013). This new information is also included in the present revision of this FGE.

2. Presentation of the Substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA Status

The JECFA has evaluated a group of 51 flavouring substances consisting of simple aliphatic and aromatic sulphides and thiols at the 68th meeting (JECFA, 2008a).

The JECFA has at the 53rd meeting, which was before 2000, evaluated a group of 137 flavouring substances consisting of simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group (JECFA, 2000).

2.1.2. EFSA Considerations

This FGE only deals with 44 of the above mentioned 188 substances: 37 substances evaluated by the JECFA at the 68th meeting, 2007, and seven substances evaluated by JECFA at the 53rd meeting, 1999 because:

- Of the 51 simple aliphatic and aromatic sulphides and thiols evaluated by the JECFA at the 68th meeting six are not in the Register (methionyl butyrate (JECFA-no: 1668), S-Ethyl 2-acetylaminoethanethionate (JECFA-no: 1680), (±)-3-(Ethyl-thio)butanol (JECFA-no: 1703), (±)-3-mercapto-1-butyl acetate (JECFA-no: 1705), 3-mercapto-3-methyl-1-butyl acetate (JECFA-no: 1706), 2,5-dithiahexane (JECFA-no: 1707) and five substances have already been evaluated in FGE.08 [FL-no: 12.120, 12.165, 12.191, 12.199 and 12.214]. The remaining 40 substances from the 68th meeting were considered in FGE.91 and FGE.91Rev1. Since the publication of FGE.91Rev1, three of the 40 candidate substances are no longer supported for use as flavouring substances in Europe by Industry (DG SANCO, 2013a). Accordingly only 37 substances from this JECFA group are considered in revision of FGE.91 (FGE.91Rev2).

- Of the 137 simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group evaluated by the JECFA at the 53rd meeting five are tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145] used as supporting substances in FGE.08 and following revisions. These substances were evaluated by the JECFA before the year 2000. For flavouring substances evaluated by the JECFA before 2000 it is laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000) that if they are considered acceptable, at the estimated levels of intake, by the JECFA and comply with the general use criteria, they could be included in the list of authorised substances without undergoing a separate evaluation for the time being. However, in FGE.08Rev1 the genotoxicity issues that were noted for

candidate tertiary thiols are obviously also of relevance for the five supporting JECFA-evaluated tertiary thiols in FGE.08Rev1. Furthermore, two of the 137 substances are acyclic sulphides [FL-no: 12.077 and 12.162], which the JECFA evaluated at step B5; No NOAEL exists to provide a margin of safety, but as the estimated intake in the USA of 0.02 and 0.4 µg/*capita*/day, respectively, are below the threshold of concern of 1.5 µg/person/day the JECFA Committee would not expect the two substances to present a safety concern when used as flavouring substances. However, in line with the opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 µg/person/day. Accordingly, these seven substances (i.e. 5 tertiary thiols and two sulphides) from the 53rd meeting are also considered.

The Panel concluded that the substances in the JECFA flavouring groups of simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group are structurally related to the group of aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA FGE.08Rev5.

The substances in FGE.08 and the following revisions were divided into subgroups. The 44 JECFA evaluated substances considered here, have been assigned to the following six EFSA defined subgroups:

I *Acyclic sulphides*

III *Monothiols, including tertiary monothiols*

IV *Dithiols*

V *Acyclic and cyclic disulphides*

VII *Mono-, di-, tri- and polysulphides with thioacetal structure*

VIII *Thioesters*

None of the substances in the current FGE are related to subgroup II, VI, IX, X and XI from FGE.08Rev5.

2.2. Isomers

2.2.1. Status

The following 21 substances [FL-no: 12.038, 12.085, 12.108, 12.252, 12.259, 12.264, 12.267, 12.273, 12.274, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.297, 15.049 and 17.036] in the group of JECFA evaluated simple aliphatic and aromatic sulphides and thiols have a chiral centre. Furthermore one substance [FL-no: 12.265] can exist as geometrical isomers.

2.2.2. EFSA Considerations

Adequate information on the isomeric composition is available for all of these 21 substances (Table 1).

2.3. Specifications

2.3.1. Status

The European Flavour Industry has submitted specifications for the substances commercially used in Europe (EFFA, 2004; EFFA, 2006; EFFA, 2010; EFFA, 2011b; Flavour Industry, 2004; Flavour Industry, 2005; Flavour Industry, 2006; Flavour Industry, 2007a; Flavour Industry, 2007b). Although the JECFA specifications are available, the specifications used in this consideration are those submitted by the Industry for the 37 substances considered by the JECFA at the 68th meeting. For the

remaining seven substances (from 53rd meeting) the JECFA specifications are used (JECFA, 1999b). See Table 1.

2.3.2. EFSA Considerations

Specifications including complete purity criteria and identity tests are available for all 44 substances.. The Panel noted that candidate substance 3-(methylthio)heptenal [FL-no: 12.273] may contain up to 5-7 % of an α,β-unsaturated aldehyde 2-(E)-heptenal [FL-no: 05.150].

3. Intake Estimation

3.1. Status

For all substances evaluated through the JECFA Procedure production volumes, based on which MSDI values can be calculated, are available for EU (JECFA, 2008a; EFFA, 2011a; IOFI, 2012) (see Table 7).

3.2. EFSA Considerations

Of the in total 44 substances evaluated through the JECFA Procedure, 39 substances have intake data for the EU available from the JECFA evaluation (JECFA, 2008a; EFFA, 2011a) and for five substances [FL-no: 12.137, 12.138, 12.145, 12.284 and 17.036] the Industry has submitted production figures for EU to EFSA. These data have been used in the present consideration (see Appendix A, Table A.2 and Table 7).

For 34 substances normal and maximum use levels have been provided by the Flavour Industry (EFFA, 2004; EFFA, 2006; Flavour Industry, 2004; Flavour Industry, 2005; Flavour Industry, 2006; Flavour Industry, 2007a) in accordance with the Commission Regulation (EC) No 1565/2000 (EC, 2000) (see Appendix A, Table A.1). Based on the normal use levels, mTAMDI figures can be calculated (for calculation of mTAMDI figures, see e.g. Annex II in (EFSA, 2004).

The mTAMDI figures calculated for five substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural classes (see Appendix A, Table A.1). For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For 10 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267 and 17.036] use levels are still needed to calculate the mTAMDI values in order to identify those flavouring substances that need a more refined exposure assessment and to finalise the evaluation.

SUMMARY OF SPECIFICATION DATA

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2008b)

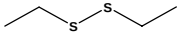
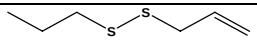
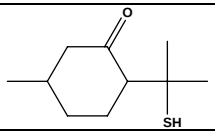
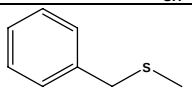
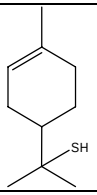
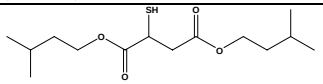
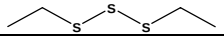
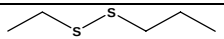
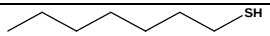
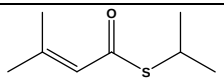
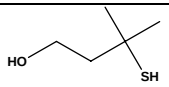
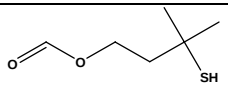
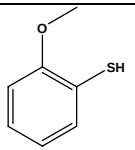
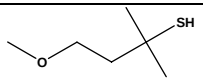
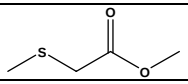
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [a] Solubility in ethanol [b]	Boiling point, °C [c] Melting point, °C ID test Assay minimum	Refrac. Index [d] Spec.gravity [e]	EFSA comments / Reference for specifications
12.012 1699	Diethyl disulfide		533 110-81-6	Liquid $C_4H_{10}S_2$ 122.24	Practically insoluble or insoluble Soluble	152 IR MS 95 %	1.502-1.508 0.990-0.996	(EFFA, 2004).
12.017 1659	Ethanethiol		546 75-08-1	Liquid C_2H_6S 62.13	Slightly soluble Soluble	35 IR NMR MS 95 %	1.425-1.431 0.833-0.839	(EFFA, 2004).
12.021 1700	Allyl propyl disulfide		4073 600 2179-59-1	Liquid $C_6H_{12}S_2$ 148.28	Practically insoluble or insoluble Soluble	66 (13 hPa) NMR MS 95 %	1.497-1.517 0.999-1.005	(EFFA, 2004).
12.038 561	8-Mercapto-p-menthan-3-one		3177 11789 38462-22-5	Liquid $C_{10}H_{18}OS$ 186.31	Insoluble Soluble	120 (13 hPa) IR 97 %	1.492-1.509 0.995-1.010	(JECFA, 1999b). Mixture of four diastereoisomers, each about 25 % (EFFA, 2014).
12.077 460	Benzyl methyl sulfide		3597 766-92-7	Liquid $C_8H_{10}S$ 138.23	Slightly soluble Soluble	197 IR 98 %	1.563-1.573 1.015-1.020	(JECFA, 1999b; EFFA, 2011b).
12.085 523	p-Menth-1-ene-8-thiol		3700 71159-90-5	Liquid $C_{10}H_{18}S$ 170.31	Slightly soluble Soluble	58 (0.4 hPa) IR 98 %	1.504 0.948 (20°)	(JECFA, 1999b). Racemate (EFFA, 2014).
12.108 1672	Di-isopentyl thiomalate		11454 68084-03-7	Solid $C_{14}H_{26}O_4S$ 290.42	Practically insoluble or insoluble Soluble	425 50 NMR MS 95 %	n.a. n.a.	Specifications (EFFA, 2004). Racemate (EFFA, 2010).
12.114	Diethyl trisulfide		4029	Liquid	Practically	217	1.556-1.560	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2008b)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [(a)] Solubility in ethanol [(b)]	Boiling point, °C [(c)] Melting point, °C ID test Assay minimum	Refrac. Index [(d)] Spec.gravity [(e)]	EFSA comments / Reference for specifications
1701			11451 3600-24-6	$C_4H_{10}S_3$ 154.3	insoluble or insoluble Soluble	 NMR MS 95 %	1.121-1.231	(EFFA, 2006).
12.126 1694	Ethyl propyl disulfide		4041 11478 30453-31-7	Liquid $C_5H_{12}S_2$ 136.27	Practically insoluble or insoluble Soluble	180 IR NMR MS 95 %	1.483-1.493 0.943-0.953	(EFFA, 2006).
12.130 1663	Heptane-1-thiol		4259 11485 1639-09-4	Liquid $C_7H_{16}S$ 132.26	Practically insoluble or insoluble Soluble	175 IR NMR MS 95 %	1.497-1.503 0.840-.0846	(EFFA, 2004).
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		4260 34365-79-2	Liquid $C_8H_{14}OS$ 158.26	Practically insoluble or insoluble Soluble	236 NMR 95 %	1.486-1.492 1.006-1.012	(EFFA, 2004).
12.137 544	3-Mercapto-3-methylbutan-1-ol		3854 34300-94-2	Liquid $C_5H_{12}OS$ 120.2	Soluble Soluble	186 (950 hPa) NMR MS 96 %	1.480-1.490 0.989 (20°)	(JECFA, 1999b).
12.138 549	3-Mercapto-3-methylbutyl formate		3855 50746-10-6	Liquid $C_6H_{12}O_2S$ 148.22	Soluble Soluble	181 IR 95 %	1.462-1.472 1.03	(JECFA, 1999b).
12.139 1666	2-Mercaptoanisole		4159 11880 7217-59-6	Liquid C_7H_8OS 140.2	Practically insoluble or insoluble Soluble	227 IR NMR MS 95 %	1.589-1.595 1.137-1.149	(EFFA, 2006).
12.145 548	4-Methoxy-2-methylbutane-2-thiol		3785 94087-83-9	Liquid $C_6H_{14}OS$ 134.24	Insoluble Soluble	59 IR 98 %	1.445-1.455 0.907-0.923	(JECFA, 1999b).
12.146 1691	Methyl (methylthio)acetate		4003 11525 16630-66-3	Liquid $C_4H_8O_2S$ 120.2	Practically insoluble or insoluble	145 IR NMR MS	1.464-1.466 1.105-1.115	(EFFA, 2006).

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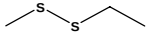
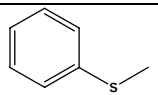
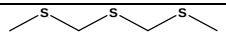
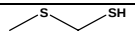
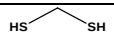
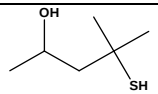
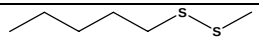
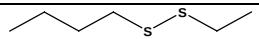
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [(a)] Solubility in ethanol [(b)]	Boiling point, °C [(c)] Melting point, °C ID test Assay minimum	Refrac. Index [(d)] Spec.gravity [(e)]	EFSA comments / Reference for specifications
					Soluble	98 %		
12.153 1693	Methyl ethyl disulfide		4040 11470 20333-39-5	Liquid $C_3H_8S_2$ 108.22	Practically insoluble or insoluble Soluble	137 IR NMR MS 80 %	1.410-1.418 1.015-1.029	Min. Assay value 80 %. Secondary components are 7-8 % diethyl sulfide and 8-10 % dimethyl sulfide. (EFFA, 2006; EFFA, 2011b).
12.162 459	Methyl phenyl sulfide		3873 11533 100-68-5	Liquid C_7H_8S 124.21	Insoluble Soluble	188-193 IR 98 %	1.532-1.551 0.958-0.968	(JECFA, 1999b; EFFA, 2011b).
12.240 1684	2,4,6-Trithiaheptane		4214 6540-86-9	Liquid $C_4H_{10}S_3$ 154.32	Slightly soluble Soluble	255 IR NMR MS 95 %	1.444-1.445 1.540-1.550	(EFFA, 2006).
12.242 1675	Methylthiomethylmercaptan		4185 29414-47-9	Liquid $C_2H_6S_2$ 94.2	Soluble Soluble	40 (2.7 hPa) NMR 97 %	1.552-1.556 1.040-1.046	(EFFA, 2006).
12.243 1661	Dimercaptomethane		4097 6725-64-0	Liquid CH_4S_2 80.17	Soluble Soluble	118 NMR 95 %	1.578-1.584 0.827-0.831	(EFFA, 2006).
12.252 1669	4-Mercapto-4-methyl-2-pentanol		4158 31539-84-1	Liquid $C_6H_{14}OS$ 134.26	Soluble Soluble	51 (0.1 hPa) NMR 98 %	1.463-1.468 1.154-1.158	(EFFA, 2006). Racemate (59-60 % trans and 29-30 % cis) (EFFA, 2013).
12.253 1697	Amyl methyl disulfide		4025 72437-68-4	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	198-202 IR NMR MS 97 %	1.485-1.495 0.943-0.953	Specifications (EFFA, 2006). Minimum assay (97 %) (EFFA, 2010).
12.254 1698	Butyl ethyl disulfide		4027 63986-03-8	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	202 IR NMR MS 90 %	1.492-1.502 0.950-0.968	Minimum assay (90 %). Secondary components diethyl disulfide (2-3 %) and dibutyl disulfide (5-6 %), (EFFA, 2010; EFFA, 2006).

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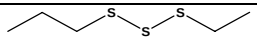
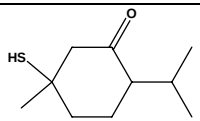
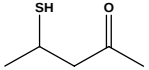
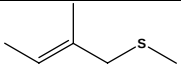
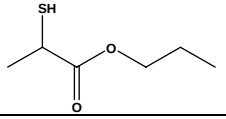
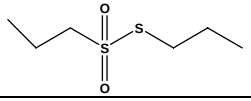
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [a] Solubility in ethanol [b]	Boiling point, °C [c] Melting point, °C ID test Assay minimum	Refrac. Index [d] Spec.gravity [e]	EFSA comments / Reference for specifications
12.256 1695	Ethyl propyl trisulfide		4042 31499-70-4	Liquid $C_5H_{12}S_3$ 168.34	Practically insoluble or insoluble Soluble	234-237 IR NMR MS 98 %	1.549-1.559 1.070-1.087	Minimum assay (98 %). Secondary components diethyl trisulfide (20-30 %) and dipropyl trisulfide (20-30 %), (EFFA, 2010; EFFA, 2006).
12.259 1673	1-Mercapto-p-menthan-3-one		4300 29725-66-4	Liquid $C_{10}H_{18}OS$ 186.31	Practically insoluble or insoluble Soluble	122 (1.3 hPa) NMR 89 %	1.487-1.497 0.989-0.999	Minimum assay (89 %) (EFFA, 2006). Cis- and trans-Mercapto-p-menthan-3-one, two cis- and two trans-enantiomers (each 25 %) Secondary components are piperitone (8-9 %) and alpha-terpineol (1-2 %). (EFFA, 2013).
12.264 1670	4,2-Thiopentanone		4157 92585-08-5	Liquid $C_5H_{10}OS$ 118.00	Insoluble Soluble	258-260 IR NMR MS 95 %	1.437-1.443 1.154-1.158	Specifications (Flavour Industry, 2006). Racemate (EFFA, 2010).
12.265 1683	2-Methyl-1-methylthio-2-butene		4173 89534-74-7	Liquid $C_6H_{12}S$ 116.23	Very slightly soluble Soluble	78 (100hPa) IR NMR MS 99.3 %	1.471 0.861	Industry has informed: 99.3 % (E)-isomer, 0.2 % (Z)-isomer, 0.2 % 1-methylthio-2-propanone, 0.1 % methyl 2-methyl-2-butenoate, 0.2 % unknown. Register name to be changed to (E)-2-Methyl-1-methylthio-2-butene (Flavour Industry, 2007b).
12.267 1667	Propyl-2-mercaptopropionate		4207 19788-50-2	Liquid $C_6H_{12}O_2S$ 148.23	Very slightly soluble Soluble	193 IR NMR MS 97.3 %	1.4497 1.018	Specifications (Flavour Industry, 2007b). Racemate (EFFA, 2010).
12.272 1702	Propyl propanethiosulfonate		4263 1113-13-9	Liquid $C_6H_{14}O_2S_2$ 182.31	Sparingly soluble Soluble	113 IR NMR MS 95 %	1.485 1.121	No longer supported by Industry (DG SANCO, 2013b). (Flavour Industry, 2007b).

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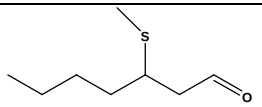
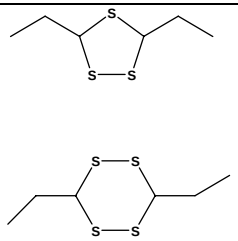
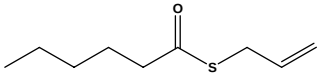
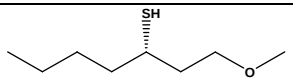
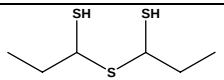
12.273 1692	3-(Methyl thio)heptanal		4183 51755-70-5	Liquid $C_8H_{16}OS$ 160.28	Insoluble Soluble	95-96 IR NMR MS 92 %	1.469-1.475 0.943-0.947	Specifications (Flavour Industry, 2006). Register name to be changed to 3-(Methyl thio)heptanal. Racemate. Minimum assay (92 %). 2-(E)-heptenal (5-7 %) (EFFA, 2010).
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		4094	Liquid $C_6H_{12}S_4/C_6H_{12}S_3$ 212.43	Insoluble Soluble	64-70 (1.3 hPa) NMR MS 95 % (1 % sol.)	1.447-1.453 0.948-0.952	Mixture of 3,6-diethyl-1,2,4,5-tetrathiane (55-60 %) (CASrn 54717-12-3) [FL-no: 15.049] and 3,5-diethyl-1,2,4-trithiolane (25-40 %) (CASrn 54644-28-9) (EFFA, 2013). Molecular weight: 212.43/180.36 (Flavour Industry, 2006). Mixture of three diastereo-isomers (EFFA, 2010). Due to the symmetry there is one meso-form (cis-form) and two trans-forms.
12.275 1681	Allylthio hexanoate		4076 156420-69-8	Liquid $C_9H_{16}OS$ 172.29	Insoluble Soluble	195-196 IR NMR MS 98 %	1.473-1.479 0.930-0.934	(Flavour Industry, 2006).
12.276 1671	(S)-1-Methoxy-3-heptanethiol		4162 400052-49-5	Liquid $C_8H_{18}OS$ 162.30	Slightly soluble Soluble	203.8 IR NMR MS 99 %	1.456-1.457 0.908-0.908	(Flavour Industry, 2007a; EFFA, 2011b).
12.284 1709	bis(1-Mercaptopropyl)sulphide		 53897-60-2	Liquid $C_6H_{14}S_3$ 182	Insoluble Soluble	225-226(101hPa) IR NMR > 98 %	1.542-1.552 1.077-1.087	Specifications (Flavour Industry, 2004).Mixture of diastereo-isomers (EFFA, 2010). Due to the symmetry there is one meso-form (50 %) and two other distereoisomers (25 % each) (EFFA, 2013).

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2008b)

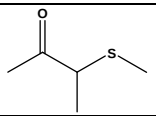
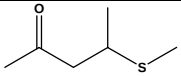
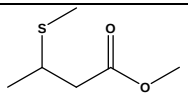
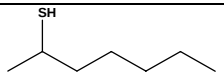
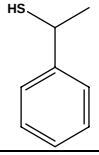
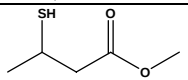
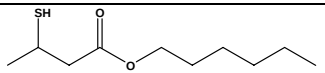
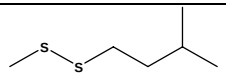
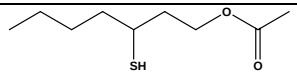
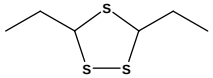
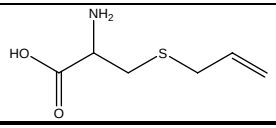
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [(a)] Solubility in ethanol [(b)]	Boiling point, °C [(c)] Melting point, °C ID test Assay minimum	Refrac. Index [(d)] Spec.gravity [(e)]	EFSA comments / Reference for specifications
12.285 1688	3-Methylthio-2-butanone		53475-15-3	Liquid $C_5H_{10}OS$ 118.2	Slightly soluble Soluble	160 IR NMR 97 %	1.468-1.4774 0.992-0.998	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.286 1689	4-Methylthio-2-pentanone		143764-28-7	Liquid $C_6H_{12}OS$ 132.22	Very slightly soluble Soluble	183 NMR MS 98 %	1.468-1.472 0.969-0.979	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.287 1690	Methyl 3-(methylthio)butanoate		4166 207983-28-6	Liquid $C_6H_{12}O_2S$ 148.22	Very slightly soluble Soluble	193 NMR 98 %	1.459-1.465 1.034-1.040	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.288 1664	Heptan-2-thiol		628-00-2	Liquid $C_7H_{16}S$ 132.27	Slightly soluble Soluble	164 NMR 98 %	1.442-1.448 0.832-0.838	Racemate (Flavour Industry, 2005).
12.289 1665	1-Phenylethylmercaptan		6263-65-6	Liquid $C_8H_{10}S$ 138.23	Practically insoluble or insoluble Soluble	199 NMR MS 98 %	1.552-1.558 1.001-1.007	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.290 1674	Methyl-3-mercaptobutanoate		4167 54051-19-3	Liquid $C_5H_{10}O_2S$ 134.20	Practically insoluble or insoluble Soluble	172 NMR 98.5 %	1.451-1.461 1.052-1.058	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.292 1704	Hexyl 3-mercaptobutanoate		4136 796857-79-9	Liquid $C_{10}H_{20}O_2S$ 204.33	Practically insoluble or insoluble Soluble	268 NMR 98 %	1.459-1.465 0.949-0.955	Specifications (Flavour Industry, 2005). Racemate (EFFA, 2010).
12.293 1660	Ethane-1,1-dithiol		69382-62-3	Liquid $C_2H_6S_2$ 94.2	Soluble Soluble	Distils: 71-78 NMR 99 %	1.369-1.375 0.829-0.833	Product is a 1 % solution of ethane-1,1-dithiol, purity 99 % min, in ethanol.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2008b)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [(a)] Solubility in ethanol [(b)]	Boiling point, °C [(c)] Melting point, °C ID test Assay minimum	Refrac. Index [(d)] Spec.gravity [(e)]	EFSA comments / Reference for specifications
12.294 1696	Isopentyl methyl disulfide		4168 72437-56-0	Liquid $C_6H_{14}S_2$ 150.31	Practically insoluble or insoluble Soluble	184-200 NMR 95 %	1.516-1.522 0.995-1.001	(Flavour Industry, 2005).
12.297 1708	3-Mercaptoheptyl acetate		4289 548774-80-7	Liquid $C_9H_{18}O_2S$ 190.30	Slightly soluble Soluble	242 IR NMR MS 99.9 %	1.4605-1.4607 0.9826-0.9830	Specifications (Flavour Industry, 2007b; EFFA, 2011b). Racemate (EFFA, 2010).
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		4030 54644-28-9	Liquid $C_6H_{12}S_3$ 180.35	Practically insoluble or insoluble Soluble	77 (0.1 hPa) NMR 95 %	1.558-1.570 1.147-1.160	Specifications (EFFA, 2006). Mixture of three diastereo-isomers (EFFA, 2010). Due to the symmetry there is one meso-form (cis-form (50 %)) and two trans-forms (25 % each) (EFFA, 2013).
17.036 1710	S-allyl-L-cysteine		4322 21593-77-1	Solid $C_6H_{11}NOS$ 161.22	Moderate soluble Slightly soluble	214-216 IR NMR MS 95 %	1.542 1.191	(Flavour Industry, 2007b).

(a): Solubility in water, if not otherwise stated.
(b): Solubility in 95 % ethanol, if not otherwise stated.
(c): At 1013.25 hPa, if not otherwise stated.
(d): At 20°C, if not otherwise stated.
(e): At 25°C, if not otherwise stated.
n.a., not available

4. Genotoxicity Data

4.1. Genotoxicity Studies – Text Taken[7] from the JECFA (JECFA, 2008a)

In vitro

No evidence of mutagenicity was observed when allylthio hexanoate [FL-no: 12.275], 3,6-diethyl-1,2,4,5-tetrathiane [FL-no: 12.274] or allyl propyl disulfide [FL-no: 12.021] were incubated with *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535 and/or TA1537 with and without metabolic activation at concentrations of up to 5000 µg/plate (Eder et al., 1980; Eder et al., 1982b; King and Harnasch, 2002; Uhde, 2005; Zeiger et al., 1988).

No evidence of mutagenicity was observed when the structurally related substances tetrahydrothiophene [FL-no: 15.102], 2-methylpropane-2-thiol [FL-no: 12.174] and methyl methanethiosulfonate [FL-no: 12.159] were incubated with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and/or TA2637 with and without metabolic activation at concentrations of up to 10 000 µg/plate (Dorange et al., 1983; Pennwalt Corporation, 1987a; Phillips Petroleum Company, 1990a).

Tetrahydrothiophene [FL-no: 15.102] tested negative in a cytogenetic assay with human lymphocytes, a mutation assay at the HPRT chromosome with Chinese hamster ovary (CHO) cells and an unscheduled deoxyribonucleic acid (DNA) synthesis test with human epithelial cells performed with and without metabolic activation at concentrations of up to 5120 µg/ml (Pennwalt Corporation, 1987a).

In the absence of an exogenous metabolic activation system, an increase was observed in the induction of forward mutations when L5178Y*tk*(+/–) mouse lymphoma cells were exposed to 2-methylpropane-2-thiol [FL-no: 12.174] at the two highest tested concentrations (i.e. 202 and 1000 µg/ml); however, in the presence of such a system, 2-methylpropane-2-thiol yielded negative results at concentrations of up to 1000 µg/ml (Phillips Petroleum Company, 1990a). Mouse lymphoma assays conducted in the absence of metabolic activation for simple aliphatic and aromatic substances have been shown to be inconsistent with the results of other standardised genotoxicity assays. Moreover, culture conditions of low pH and high osmolality have been shown to produce false-positive results in *in vitro* genotoxicity assays (Cifone et al., 1987; Galloway et al., 1987; Heck et al., 1989). Therefore, it is not unexpected that other low molecular weight thiols (e.g. ethane thiol [FL-no: 12.017] and butane-1-thiol [FL-no: 12.010]) have been shown to produce equivocal or positive evidence of mutagenicity in the mouse lymphoma forward mutation assay, while being negative in reverse mutation assays (Eder et al., 1980; Eder et al., 1982b; King and Harnasch, 2002; Uhde, 2005; Zeiger et al., 1988). Furthermore, dibutyl disulphide [FL-no: 12.111] yielded negative results in a mouse lymphoma forward mutation assay without metabolic activation; however, the concentrations tested in this trial were not specified (Dooley et al., 1987).

Tetrahydrothiophene [FL-no: 15.102] and 2-methylpropane-2-thiol [FL-no: 12.174] were negative in a sister chromatid exchange (SCE) assay with CHO cells at concentrations of up to 125 and 1350 µg/ml, respectively, with and without metabolic activation (Pennwalt Corporation, 1987a; Phillips Petroleum Company, 1990a). Although a statistically significant increase in the number of SCEs was observed at concentrations of 450 and 1350 µg 2-methylpropane-2-thiol/ml, there was a lack of significant increases at lower test concentrations. Additionally, although statistically significant, the increases in SCEs were less than 2-fold greater than in controls. As such, the authors concluded 2-methylpropane-2-thiol to be non-mutagenic (Phillips Petroleum Company, 1990a).

[7] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

Methyl methanethiosulfonate [FL-no: 12.159] was negative in chromosomal aberration assays conducted in *Saccharomyces cerevisiae* strain D7 or *S. cerevisiae* haploid strain N123 at concentrations of up to 300 µg/ml (Dorange et al., 1983).

Conclusion on genotoxicity

The testing of these representative materials *in vitro* in prokaryotic and eukaryotic test systems indicates that this group of simple aliphatic and aromatic sulphides and thiols is not expected to exhibit any mutagenic or genotoxic properties.

For a summary of *in vitro / in vivo* genotoxicity data considered by the JECFA see Table 3.

4.2. Genotoxicity Studies – Text Taken[8] from EFSA FGE. 08Rev5 (EFSA CEF Panel, 2012)

Only text from the relevant supporting subgroups (subgroup I, III, IV, V, VII and VIII) are shown here.

In vitro / in vivo

Genotoxicity *in vitro* data are available for four candidate substances: di-(1-propenyl)-sulfid (mixture) [FL-no: 12.298] (subgroup I); 2-methylpropane-2-thiol [FL-no: 12.174] (subgroup III); and dibutyl disulfide [FL-no: 12.111] (subgroup V). In addition studies are available on 12 supporting substances from subgroups I (1), III (4), IV (1), V (4) and VIII (2).

In vivo data are available for three supporting substances from subgroups I (1), III (1) and V (1).

Subgroup I (Acyclic sulphides)

In vitro data are available for the candidate substance, di-(1-propenyl)-sulfide [FL-no: 12.298]; Ames test: *S. typhimurium* TA98, TA100, TA102, TA1535, TA1537, 1-100 microg/plate. Result was negative with and without metabolic activation (Stien, 2005).

For supporting substances, only data on diallyl sulfide [FL-no: 12.088] are available: diallyl sulfide was negative in a limited bacterial reversion assay using one strain only (TA100) and provided equivocal results in an *in vitro* cytogenetic test in which increased incidences of cells with chromosomal aberrations and sister chromatid exchanges (SCEs), statistically significant but not dose related, were observed. *In vivo* diallyl sulfide was evaluated as negative in a micronucleus test in mouse bone marrow, which was, however, not designed to evaluate the genotoxicity of the substance itself as it was tested in a mixture. Overall the data available do not allow evaluation of the genotoxicity of the substances of this subgroup.

Subgroup III (Monothiols)

2-Methylpropane-2-thiol [FL-no: 12.174] is reported to be negative in an Ames test. It is reported to be positive in a mouse lymphoma assay without metabolic activation and negative in the test with metabolic activation, and it is reported to be negative in an *in vitro* SCE assay. However, these studies are reported only as summaries [Phillips Petroleum Company, 1990a]. Some details are available for methods but not for the results. Although the validity of these studies cannot be fully evaluated, the positive result in the mouse lymphoma assay raises concern with respect to the potential for genotoxicity of this tertiary thiol and structurally related compounds, i.e. 2-methylbutane-2-thiol [FL-no: 12.172] and ethyl-2-mercapto-2-methyl propanoate [FL-no: 12.304] and the five supporting substances [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145].

[8] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

The *in vitro* data available for the other substances in this subgroup do not provide indication of concern for genotoxicity.

Subgroup IV (Dithiols)

Equivocal results were reported for the only supporting substance tested. 1,2-ethanedithiol [FL-no: 12.066] was evaluated positive for induction of gene mutations and SCEs *in vitro* in a poorly reported study. However, increased mutation frequencies were associated with unacceptably high toxicity, and the relevance of SCEs for genotoxicity assessment is unclear. Moreover, the validity of the latter data set is questionable, as the distinct effect of S9 on toxicity observed in the other mammalian cell mutation study was not replicated. 1,2-ethanedithiol [FL-no: 12.066] was reported in an abstract to be negative in the Ames test.

Subgroup V (Acyclic and Cyclic dipolysulphides)

Dibutyl disulfide [FL-no: 12.111] is reported to be negative in a mouse lymphoma assay (Dooley et al., 1987). However, the study is reported only as abstract, and thus, the validity cannot be evaluated.

Further data are available for the supporting substances diallyl disulfide [FL-no: 12.008], dimethyldisulfide [FL-no: 12.026], phenyl disulfide [FL-no: 12.043] and benzyl disulfide [FL-no: 12.081]. All substances were negative in the Ames test. In addition, diallyl disulfide was reported to be positive in a chromosomal aberration assay *in vitro*, with and without metabolic activation, and weakly positive in a SCE assay. However, the validity of these findings is doubtful as chromosomal aberrations were only increased in conditions associated with extensive (> 90 %) lethality, and because of the limitation of SCE in genotoxic hazard identification.

Subgroup VII (Mono-, di-, tri- and polysulphides with thioacetal structure)

There are no data available on genotoxicity for the substances in this group. However, one of the hydrolysis products of the candidate substance 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057] is structurally related to the above-mentioned tertiary thiols, raising concern with respect to the genotoxicity of this candidate. Therefore, in the absence of further genotoxicity data, the Panel concluded that the Procedure could not be applied to 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057].

Subgroup VIII (Thioesters)

The *in vitro* data available on supporting substances provide no indication of concern for genotoxicity.

Conclusion on genotoxicity

Most *in vitro* and *in vivo* studies are of limited or insufficient quality and provide only limited information.

The available data raise concern with respect to genotoxicity of three tertiary thiols [FL-no: 12.172, 12.174 and 12.304], included as candidate substances in subgroup III. Hydrolysis of the candidate substance 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057], included in subgroup VII, leads to the formation of a tertiary thiol structurally related to the above-mentioned compounds. Therefore, there is also concern with respect to genotoxicity of this candidate substance. The Panel noted that in FGE.08 five of the supporting substances were tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138 and 12.145] for which a concern for genotoxicity has been raised in the FGE.08Rev1. These supporting substances have been evaluated by the JECFA at the 53rd meeting (JECFA, 2000b; JECFA, 2000). These supporting substances have been considered by EFSA in FGE.91 (EFSA CEF Panel, 2010q).

In addition, genotoxicity of the candidate substance methyl methanethiosulphonate [FL-no: 12.159], included in subgroup X, could not be assessed from the data available. However, due to the similarity

with methyl methanesulphonate, a direct acting mutagen and carcinogen, there is concern with respect to genotoxic potential of this candidate substance.

Therefore, the Panel decided that the Procedure could not be applied to the candidate substances [FL-no: 12.159, 12.172, 12.174, 12.304 and 16.057] until adequate *in vivo* genotoxicity data become available.

The other *in vitro/in vivo* genotoxicity data available, often from limited or poorly reported studies, do not provide clear indication of concern for genotoxicity for the remaining candidate substances included in the present evaluation.

For a summary of *in vitro / in vivo* genotoxicity data considered by EFSA in FGE.08Rev5, see Table 4 and Table 5.

4.3. EFSA Considerations

Subgroup III includes the tertiary thiols for which a genotoxicity concern was established based on data from a limited gene mutation assay for candidate substances FGE.08Rev1 [FL-no: 12.174] and additional genotoxicity data were requested for this group of substances. Since the publication of the latest revision of FGE.08, FGE.08Rev5 the Industry has submitted a new bacterial mutation assay for the tertiary thiol [FL-no: 12.169] included in FGE.91. This substance is considered by the Panel to be representative for the whole group of tertiary thiols (in FGE.08, FGE.74 and FGE.91). Based on the new genotoxicity data the Panel concluded that 2-methyl-4-oxopentane-2-thiol [FL-no: 12.169] was not genotoxic in the assay and that 2-methyl-4-oxopentane-2-thiol [FL-no: 12.169] does no longer give rise to concern with respect to gene mutations. The Panel therefore concluded that the tertiary thiols, including the substances in FGE.91Rev2 [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] can be evaluated using the Procedure.

Although the available data are limited[9] the Panel considered that for the 44 substances in FGE.91Rev2 the genotoxicity data do not preclude evaluating these substances through the Procedure.

However, the Panel noted that candidate substance 3-(methylthio)heptenal [FL-no: 12.273] may contain up to 5-7 % of an α,β -unsaturated aldehyde (2-(E)-heptenal [FL-no: 05.150] for which a concern has been raised due to the presence of a structural alert for genotoxicity. This substance is a candidate flavouring substance [FL-no: 05.150] which is under evaluation in FGE.200Rev1 (FGE.19 subgroup 1.1.1).

5. Application of the Procedure

5.1. Application of the Procedure to Simple Aliphatic and Aromatic Sulphides and Thiols by the JECFA (JECFA, 2000; JECFA, 2008a)

Note: The JECFA evaluated substances not in the Register, are identified by their four digit JECFA number in the following text.

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents to these 44 flavouring agents considered in this FGE, the Committee assigned 31 [FL-no: 12.012, 12.017, , 12.126, 12.130, 12.134, 12.137, 12.138, 12.145, 12.146, 12.153, 12.240, 12.242, 12.243, 12.252, 12.253, 12.254, 12.264, 12.265, 12.267, 12.273, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12,290, 12.292, 12.293, 12.294 and 12.297] to structural class I and 10 [FL-no: 12.021, 12.038, 12.077, 12.085, 12.162, 12.259, 12.274, 12.275, 12.289 and 15.049] to structural class II. The remaining three

[9] The Panel noted that few days before the adoption of the Opinion EFFA provided a new in vivo micronucleus study on [FL-no:12.169] which will be considered in the next revision of this Opinion

flavouring agents [FL-no: 12.108, 12.139 and 17.036] were assigned to structural class III (Cramer et al., 1978).

Step 2

None of the flavouring agents in this group can be predicted to be metabolised to innocuous products. The evaluation of these substances therefore proceeded via the B-side of the Procedure.

Step B3

The estimated daily per capita intakes of the 31 flavouring agents in this group in structural class I are below the threshold of concern (i.e. 1800 µg/person per day for class I). The estimated daily per capita intakes of the 10 flavouring agents in structural class II are below the threshold of concern (i.e. 540 µg/person per day for class II). The estimated daily per capita intakes of the three flavouring agents in structural class III are below the threshold of concern (i.e. 90 µg/person per day for class III). Accordingly, the evaluation of all the substances in the group proceeded to Step B4.

Step B4

For 2-methyl-1-methylthio-2-butene [FL-no: 12.265], the no-observed effect level (NOEL) of 250 mg/kg body weight (bw) per day for the structurally related substance methyl sulfide [FL-no: 12.006] from a 98-day study in male and female rats (Butterworth et al., 1975) provides an adequate margin of safety (at least 125 million) in relation to currently estimated levels of intake of this substance from its use as a flavouring substance. This NOEL is also appropriate for the structurally related substances 2,4,6-trithiaheptane [FL-no: 12.240] and 2,5-dithiahexane (No. 1707), because they are all simple sulfides that are anticipated to undergo oxidation and subsequent metabolism via similar metabolic pathways. In relation to the currently estimated levels of intake from use as flavouring substances, the NOEL of 250 mg/kg bw per day provides adequate margins of safety of > 1 billion[10] and 125 million for 2,4,6-trithiaheptane [FL-no: 12.240] and 2,5-dithiahexane (No. 1707), respectively.

For methionyl butyrate (No. 1668), the NOEL of 1.4 mg/kg bw per day for the structurally related substance 2-(methylthiomethyl)-3-phenylpropenal [FL-no: 12.087] from a 92-day study in male rats (Cox et al., 1979) provides an adequate margin of safety (7 million) in relation to currently estimated levels of intake of this substance from its use as a flavouring substance. This NOEL is also appropriate for the structurally related substances (±)-isobutyl 3-methylthiobutyrate [FL-no: 12.214], methyl (methylthio)acetate [FL-no: 12.146] and (±)-3-(methylthio)heptanal [FL-no: 12.273], because they are all acyclic sulfides with oxidized sidechains. For these structurally related substances, the NOEL of 1.4 mg/ kg bw per day provides adequate margins of safety in the range of 28 000 to 7 million in relation to the currently estimated levels of intake from use as flavouring agents.

For methylthiomethylmercaptan [FL-no: 12.242], the NOEL of 0.3 mg/kg bw per day for the structurally related substance 3-methyl-1,2,4-trithiane [FL-no: 15.036] from a 90-day study in rats (Mondino, 1981) provides an adequate margin of safety (at least 150 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For 3-(methylthio)-2-butanone [FL-no: 12.285] and (±)-3-(ethylthio)butanol (No. 1703), the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2-mercapto-3-butanol [FL-no: 12.024] from a 90-day study in rats (Cox et al., 1974a) provides adequate margins of safety (> 3 million and 350 000, respectively) in relation to estimated levels of intake of these substances from their use as flavouring agents.

For 4-(methylthio)-2-pentanone [FL-no: 12.286], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3-mercapto-2-pentanone [FL-no: 12.031] from a 90-day study in rats

[10] Note that billion is defined as (10^9).

(Morgareidge, 1971) provides an adequate margin of safety (> 9 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For methyl 3-(methylthio)butanoate [FL-no: 12.287], the NOEL of 6.5 mg/ kg bw per day for the structurally related substance ethyl thioacetate [FL-no: 12.018] from a 91-day study in rats (Shellenberger, 1970) provides an adequate margin of safety (> 32 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For *S*-allyl-L-cysteine [FL-no: 17.036], the NOEL of 250 mg/kg bw per day from a 28-day study in rats (Kodera et al., 2002) provides an adequate margin of safety (> 8 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For (±)-2,8-epithio-*cis*-*p*-menthane [FL-no: 12.120], the NOEL of 10 mg/kg bw per day in female rats from a 28-day study (Finlay, 2004) provides an adequate margin of safety (> 1 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethanethiol [FL-no: 12.017], the NOEL of 0.56 mg/kg bw per day for the structurally related substance cyclopentanethiol [FL-no: 12.029] from a 90-day study in male and female rats (Morgareidge and Oser, 1970a) provides an adequate margin of safety (at least 80 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances 1-pentanethiol [FL-no: 12.191], 1-heptanethiol [FL-no: 12.130] and 2-heptanethiol [FL-no: 12.288], because they are all simple thiols. For these structurally related substances, the NOEL of 0.56 mg/ kg bw per day provides adequate margins of safety in the range of > 100 000 to > 2 million in relation to the currently estimated levels of intake from use as flavouring agents.

For (±)-1-phenylethylmercaptan [FL-no: 12.289], the NOEL of 0.43 mg/ kg bw per day for the structurally related substance 2,6-dimethylthiophenol [FL-no: 12.082] from a 90-day study in rats (Peano et al., 1981) provides an adequate margin of safety (> 2 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For propyl 2-mercaptopropionate [FL-no: 12.267], the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2-mercapto-3-butanol [FL-no: 12.024] from a 90-day study in rats (Cox et al., 1974a) provides an adequate margin of safety (at least 350 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances (±)-4-mercapto-4-methyl-2-pentanol [FL-no: 12.252], (*S*)-1-methoxy-3-heptanethiol [FL-no: 12.276], methyl 3-mercaptobutanoate [FL-no: 12.290]), hexyl 3-mercaptobutanoate [FL-no: 12.292], (±)-3-mercapto-1-butyl acetate (No. 1705), 3-mercapto-3-methyl-1-butyl acetate (No. 1706), 3-mercaptoheptyl acetate [FL-no: 12.297] and *cis*-and *trans*-mercapto-*p*-menthan-3-one [FL-no: 12.259], because they are all thiols with oxidized side-chains. For these structurally related substances, the NOEL of 0.7 mg/kg bw per day provides adequate margins of safety in the range of > 23 000 to > 3 million in relation to the currently estimated intakes from use as flavouring agents.

For 4-mercapto-2-pentanone [FL-no: 12.264], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3-mercapto-2-pentanone [FL-no: 12.031] from a 90-day study in rats (Morgareidge, 1971) provides an adequate margin of safety (> 1 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For 2-mercaptoanisole [FL-no: 12.139], the NOEL of 0.51 mg/kg bw per day for the structurally related substance 2-mercaptomethylbenzene [FL-no: 12.027] from a 90-day study in rats (Posternak et al., 1969) provides an adequate margin of safety (at least 25 500) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethane-1,1-dithiol [FL-no: 12.293], the NOEL of 125 mg/kg bw per day for one hydrolysis product, acetaldehyde [FL-no: 05.001], from a 28-day study in rats (Til et al., 1988) and the NOEL of 6.5 mg/kg bw per day for the other hydrolysis product, hydrogen sulfide, from a 90-day inhalation study in rats (Chemical Industry Institute of Technology, 1983) provide adequate margins of safety (625 million and > 32 million, respectively) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For dimercaptomethane [FL-no: 12.243], the NOEL of 15 mg/kg bw per day for one hydrolysis product, formaldehyde, from a 2-year study in rats (Til et al., 1989) and the NOEL of 6.5 mg/kg bw per day for the other hydrolysis product, hydrogen sulfide, from a 90-day inhalation study in rats (Chemical Industry Institute of Technology, 1983) provide adequate margins of safety (75 million and > 32 million, respectively) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For bis(1-mercaptopropyl)sulfide [FL-no: 12.284], the NOEL of 0.7 mg/kg bw per day for the structurally related substance 2,3-butanedithiol [FL-no: 12.022] from a 90-day study in rats (Morgareidge, 1974) provides an adequate margin of safety (70 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For ethyl methyl disulfide [FL-no: 12.153], the NOEL of 7.3 mg/kg bw per day for the structurally related substance propyl disulfide [FL-no: 12.014] from a 90-day study in rats (Posternak et al., 1969) provides an adequate margin of safety (> 14 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances ethyl propyl disulfide [FL-no: 12.126], methyl isopentyl disulfide [FL-no: 12.294], amyl methyl disulfide [FL-no: 12.253], butyl ethyl disulfide [FL-no: 12.254] and diethyl disulfide [FL-no: 12.012], because they are all simple disulfides. For these structurally related substances, the NOEL of 7.3 mg/kg bw per day provides adequate margins of safety in the range of > 14 million to > 36 million in relation to the currently estimated intakes of these substances from use as flavouring agents.

For allyl propyl disulfide [FL-no: 12.021], the NOEL of 4.6 mg/kg bw per day for the structurally related substance diallyl trisulphide [FL-no: 12.009] from a 90-day study in rats (Morgareidge and Oser, 1970b) provides an adequate margin of safety (> 4 million) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For 3,5-diethyl-1,2,4-trithiolane [FL-no: 15.049], the NOEL of 1.9 mg/kg bw per day for the structurally related substance 3,5-dimethyl-1,2,4-trithiolane [FL-no: 15.025] from a 91-day study in rats (BIBRA, 1976) provides an adequate margin of safety (at least 190 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For the mixture of 3,6-diethyl-1,2,4,5-tetrathiane (approximately 55 %) and 3,5-diethyl-1,2,4-trithiolane (approximately 45 %) [FL-no: 12.274], the NOEL of 0.3 mg/kg bw per day for the structurally related substance 3-methyl-1,2,4-trithiane [FL-no: 15.036] from a 90-day study in rats (Mondino, 1981) provides an adequate margin of safety (30 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent.

For thioacetic acid [FL-no: 12.199], the NOEL of 6.5 mg/kg bw per day for the structurally related substance ethyl thioacetate [FL-no: 12.018] from a 91-day study in rats (Shellenberger, 1970) provides an adequate margin of safety (> 900 000) in relation to currently estimated levels of intake of this substance from use as a flavouring agent. This NOEL is also appropriate for the structurally related substances *S*-methyl propanethioate [FL-no: 12.165], *S*-isopropyl 3-methylbut-2-enethioate [FL-no: 12.134], allylthio hexanoate [FL-no: 12.275] and *S*-ethyl 2-acetylamino ethan-ethioate (No. 1680), because they are all thioesters and related acids. For these structurally related substances, the NOEL of 6.5 mg/kg bw per day provides adequate margins of safety in the range of > 3 million to > 32 million in relation to their currently estimated levels of intake from their use as flavouring agents.

For 1-p-menthene-8-thiol [FL-no: 12.085] a NOEL of 0.56 mg/kg bw per day was reported in a 90-day study in rats treated with cyclopentanethiol [FL-no: 12.029] only at that dose (Morgareidge and Oser, 1970a).

For the four thiols with oxygenated side-chains [FL-no: 12.038, 12.137, 12.138, 12.145], NOELs are available for three substances (1.9 mg/kg bw per day for 2-mercapto-3-butanol [FL-no: 12.024] (JECFA No. 546), 2.8 mg/kg bw per day for alpha-methyl-beta-hydroxypropyl alpha-methyl-beta-mercaptopropyl sulfide [FL-no: 12.036] (JECFA No. 547), and 1.9 mg/kg bw per day for 3-mercapto-2-pentanone [FL-no: 12.031] (JECFA No. 560)). These NOELs were considered to provide adequate safety margins for the flavouring agents in this subgroup.

No adequate NOEL was available for benzyl methyl sulphide and methyl phenyl sulphide [FL-no: 12.077 and 12.162] or a related substance, therefore no adequate margin of safety can be provided. Therefore evaluation of the substance proceeds with step B5.

Step B5

Three substances, diisopentyl thiomalate [FL-no: 12.108],], benzyl methyl sulphide [FL-no: 12.077] and methyl phenyl sulphide [FL-no: 12.162] were evaluated at this step of the Procedure. The currently estimated daily per capita intakes of all three substances are below 1.5 µg/person per day in Europe. Applying the criteria for Step B5 outlined in Annex 5 of the evaluations published after its forty-ninth meeting, the Committee concluded that the use of these substances as flavouring agents at their currently estimated levels of intake poses no safety concern.

The stepwise evaluations of the substances evaluated by the JECFA are summarised in Table 6.

5.2. Application of the Procedure to Aliphatic and Alicyclic Mono-, Di-, Tri-, and Polysulphides with or without Additional Oxygenated Functional Groups by EFSA in FGE.08Rev5 (EFSA CEF Panel, 2012)[11]

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach.

For the candidate substance methyl methanethiosulphonate [FL-no: 12.159] (the only substance in subgroup X), there is an indication of a genotoxic potential *in vitro*. Furthermore, for three candidate substances (in subgroup III), 2-methylbutane-2-thiol [FL-no: 12.172], 2-methylpropane-2-thiol [FL-no: 12.174] and ethyl-2-mercapto-2-methyl propanoate [FL-no: 12.304] and one candidate substance (in subgroup VII), 2,4,4-trimethyl-1,3-oxathiane [FL-no: 16.057], a concern for genotoxicity was also identified based on experimental evidence for [FL-no: 12.174] and the structural similarity among these four substances. Therefore, in the absence of further genotoxicity data, the Panel concluded that the Procedure could not be applied to these five substances.

For four candidate substances, 3-mercaptooctanal [FL-no: 12.268] (subgroup III), 3-mercaptodecanal [FL-no: 12.269] (subgroup III), methanedithiol diacetate [FL-no: 12.271] (subgroup VIII) and 3,5-dimethyl-1,2-dithiolane-4-one [FL-no: 12.295] (subgroup V) no data on use as flavouring substances in Europe are available. Therefore, no intakes in Europe can be estimated and accordingly the Panel concluded that the Procedure could not be applied to these four substances.

Thus, for in total nine candidate substances the Procedure could not be applied: [FL-no: 12.159, 12.172, 12.174, 12.268, 12.269, 12.271, 12.295, 12.304 and 16.057].

For the safety evaluation of the remaining 71 candidate substances from chemical groups 20 and 30 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the 71 substances evaluated through the Procedure are summarised in Table8.

[11] The text is taken verbatim from the indicated reference source, but text related to subgroups not included in the present FGE has been removed

Step 1

The candidate substances were classified following the procedure established by Cramer et al. (Cramer et al., 1978). For the 71 candidate substances evaluated through the Procedure, 42 substances were classified into structural class I, 19 substances were classified into structural class II and 10 substances were classified into structural class III.

Step 2

Step 2 requires consideration of whether metabolic pathways exist to metabolise the candidate substances to innocuous products at the expected levels of intake. The candidate substances may be biotransformed to reactive metabolites, such as thiols, sulphoxides and sulphones and, in consequence, they are not predicted to be metabolised to innocuous products. Therefore, the evaluation of all 71 candidate substances proceeds via the B-side of the Procedure scheme.

Step B3

The 42 substances in structural class I have estimated European daily *per capita* intakes ranging from 0.0012 to 6.1 µgram, which is below the threshold of concern of 1800 µg/person/day. The 19 substances evaluated through the Procedure in structural class II have estimated European daily *per capita* intakes ranging from 0.0024 to 2.4 µg, which is below the threshold of concern for class II of 540 µg/person/day. The 10 substances in structural class III have estimated European daily *per capita* intakes ranging from 0.012 to 6.1 µg, which is below the threshold of concern for class III of 90 µg/person/day. Accordingly, all 71 candidate substances proceed to step B4 of the Procedure.

Step B4

No adequate studies on candidate substances are available. Repeated-dose toxicity studies are available on some supporting substances, which, with very few exceptions, have been carried out testing only one dose, giving rise to no observed adverse effects. The results of adequate studies on supporting substances show a relatively high degree of variability in the reported No Observed Adverse Effect Levels (NOAELs), ranging from 0.06 to 250 mg/kg bw/day.

The 20 candidate substances in subgroup I can be represented by the supporting substance dimethyl sulfide [FL-no:12.006], for which an adequate 90-day subchronic study is available, indicating that no adverse effects were produced by the highest oral dose tested (250 mg/kg body weight (bw)/day), which can be considered a NOAEL. The combined estimated daily *per capita* intake of 10 µg for the 20 candidate substances in subgroup I corresponds to 0.17 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.5×10^6 can be calculated. The 20 candidate substances in subgroup I are accordingly not expected to be of safety concern at the estimated levels of intake.

Within subgroup III, adequate 90-day subchronic studies are available for four supporting secondary thiols, 2-mercapto-3-butanol [FL-no: 12.024], cyclopentanethiol [FL-no: 12.029], 2-, 3- and 10-mercaptopinane [FL-no: 12.035] and 2,6-(dimethyl)thiophenol [FL-no: 12.082], which can be considered representative of the 11 candidate substances evaluated through the Procedure in this subgroup. In the four studies, no adverse effects were produced by the highest oral dose tested ranging from 0.06 up to 0.7 mg/kg bw/day. By adopting a conservative approach the lowest value (0.06 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily *per capita* intake of 1.13 µg for the 11 candidate substances evaluated through the Procedure in subgroup III corresponds to 0.019 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 3×10^3 can be calculated. The 11 candidate substances in subgroup III, evaluated through the Procedure are accordingly not expected to be of safety concern at the estimated levels of intake.

The two candidate substances in subgroup IV can be represented by two supporting substances, butane-2,3-dithiol [FL-no: 12.022] and octane-1,2-dithiol [FL-no: 12.034], for which adequate 90-day

subchronic studies are available. In the two studies, no adverse effects were produced by the almost identical highest oral doses tested, that is 0.7 mg/kg bw/day, which can be considered a NOAEL. The estimated daily *per capita* intake of 0.42 µg for the two candidate substances in subgroup IV corresponds to 0.005 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.4×10^5 can be calculated. The candidate substances in subgroup IV are accordingly not expected to be of safety concern at the estimated level of intake.

Within subgroup V, adequate 90-day subchronic studies are available for two supporting substances dicyclohexyl disulfide [FL-no: 12.028] and benzyl methyl disulfide [FL-no: 12.068], which can be considered representative of the four candidate substances in this subgroup evaluated through the Procedure. In the two studies, no adverse effects were produced by the highest oral dose tested: 0.23 and 1.15 mg/kg bw/day. By adopting a conservative approach, the lowest value (0.23 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily *per capita* intake of 0.6 µg for the four candidate substances evaluated through the Procedure in subgroup V corresponds to 0.010 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 2.3×10^5 can be calculated. The four candidate substances in subgroup V are accordingly not expected to be of safety concern at the estimated levels of intake.

Within subgroup VII, adequate 90-day subchronic studies are available for five supporting substances, trithioacetone [FL-no: 15.009], 3,5-dimethyl-1,2,4-trithiolane [FL-no: 15.025], 2-methyl-4-propyl-1,3-oxathiane [FL-no:16.030], 2-methyl-1,3-dithiolane [FL-no: 15.034] and 3-methyl-1,2,4-trithiane [FL-no: 15.036], which can be considered representative for 12 of the candidate substances in this subgroup. In the 90-day studies, no adverse effects were produced by the only oral dose tested, 0.2, 1.88, 0.44, 7 and 0.3 mg/kg bw/day, respectively. By adopting a conservative approach, the lowest value (0.2 mg/kg bw/day) can be considered a NOAEL. The combined estimated daily per capita intake of 3.9 µg for these 12 candidate substances in subgroup VII corresponds to 0.065 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 3.1×10^3 can be calculated. These 12 substances are not expected to be of safety concern at the estimated levels of intake.

For the remaining candidate substance in subgroup VII, 2,5-dihydroxy-1,4-dithiane [FL-no: 15.134], a 90-day study is available for the supporting substance 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane [FL-no: 15.006] that can be considered to be structurally related to this candidate substance. In the study no adverse effects were produced by the only oral dose tested, 3.14 mg/kg bw/day. Therefore the NOAEL is concluded to be 3.14 mg/kg bw/day for this supporting substance. The estimated daily *per capita* intake for the candidate substance 2,5-dihydroxy-1,4-dithiane [FL-no: 15.134] is 6.1 µg, which corresponds to 0.10 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 3.1×10^4 may be calculated. The candidate substance is accordingly not expected to be of safety concern at the estimated level of intake.

Within subgroup VIII, an adequate 90-day subchronic study is available for one supporting substance, ethyl thioacetate [FL-no: 12.018], which can be considered representative of the eight candidate substances evaluated through the Procedure in this subgroup. In the study, no adverse effects were produced by the highest oral dose tested: 6.63 mg/kg bw/day. Therefore, the NOAEL is concluded to be 6.63 mg/kg bw per day for ethyl thioacetate. The combined estimated daily *per capita* intake of 2.4 µg for the eight candidate substances in subgroup VIII corresponds to 0.04 µg/kg bw/day at a body weight of 60 kg. Thus, a margin of safety of 1.7×10^5 can be calculated. The eight candidate substances in subgroup VIII are accordingly not expected to be of safety concern at the estimated levels of intake.

The conclusion from step B4 is that for the 58 candidate substances belonging to subgroups I, III, IV, V, VII and VIII and evaluated through the Procedure, adequate NOAELs exist for the candidate substance or for structurally related substances providing adequate margins of safety at the estimated levels of intake. Therefore, these candidate substances are not expected to be of safety concern at the levels of exposure estimated by the MSDI approach.

The evaluations of the aliphatic and alicyclic thiols, mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups of FGE.08Rev5 are summarised in Table 8

5.3. EFSA Considerations

The 44 JECFA evaluated simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group are distributed into six subgroups of structurally related substances. The subgrouping is the same as used in FGE.08Rev5. See Section 2.1.2 and Table 2.

A new bacterial gene mutation assay for 2-methyl-4-oxopentane-2-thiol [FL-no: 12.169] in FGE.74Rev3 has become available. This substance is considered to be supporting for the seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] in FGE.91. Based on these data the Panel considered that the seven tertiary thiols in FGE.91Rev2 can be evaluated through the Procedure.

Table 2: The Subgrouping of the 44 Simple Aliphatic and Aromatic Sulfides and Thiols in FGE.91Rev2.

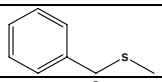
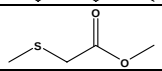
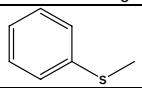
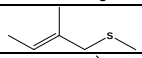
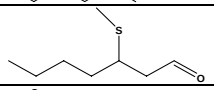
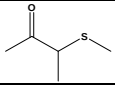
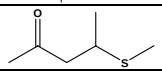
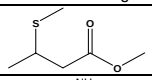
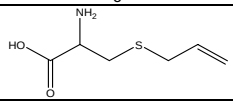
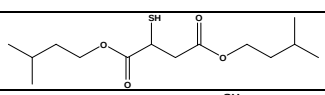
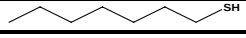
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
I Acyclic sulphides In FGE.08Rev5 this subgroup was represented by supporting substance [FL-no: 12.006], for which an adequate NOAEL is available (Butterworth et al., 1975).			
12.077 460	Benzyl methyl sulphide		II
12.146 1691	Methyl (methylthio)acetate		I
12.162 459	Methyl phenyl sulphide		II
12.265 1683	2-Methyl-1-methylthio-2-butene		I
12.273 1692	3-(Methyl-thio)heptanal		I
12.285 1688	3-Methylthio-2-butanone		I
12.286 1689	4-Methylthio-2-pentanone		I
12.287 1690	Methyl 3-(methylthio)butanoate		I
17.036 1710	S-allyl-L-cysteine		III
III Monothiols (including tertiary monothiols) In FGE.08Rev5 the secondary monothiols were represented by supporting substances [FL-no: 12.024, 12.029, 12.035, 12.082] for which adequate toxicological studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al., 1974a; Morgareidge and Oser, 1970a; Oser, 1966; Peano et al., 1981).			
12.017 1659	Ethanethiol		I
12.108 1672	Di-isopentyl thiomalate		III
12.130	Heptane-1-thiol		I

Table 2: The Subgrouping of the 44 Simple Aliphatic and Aromatic Sulfides and Thiols in FGE.91Rev2.

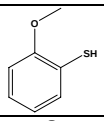
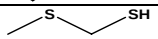
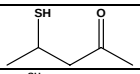
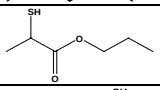
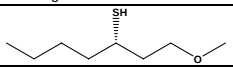
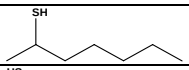
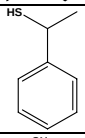
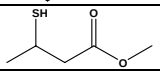
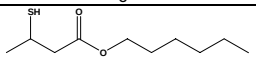
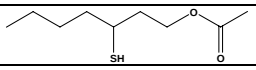
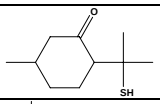
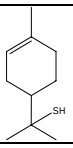
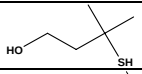
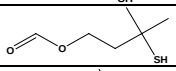
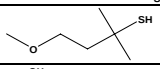
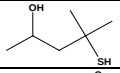
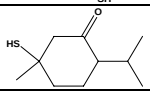
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
1663			
12.139 1666	2-Mercaptoanisole		III
12.242 1675	Methylthiomethylmercaptan		I
12.264 1670	4,2-Thiopentanone		I
12.267 1667	Propyl-2-mercaptopropionate		I
12.276 1671	(S)-1-Methoxy-3-heptanethiol		I
12.288 1664	Heptan-2-thiol		I
12.289 1665	1-Phenylethylmercaptan		II
12.290 1674	Methyl-3-mercaptobutanoate		I
12.292 1704	Hexyl 3-mercaptobutanoate		I
12.297 1708	3-Mercaptoheptyl acetate		I
Tertiary Monothiols Concern for genotoxic potential has been ruled out. No NOAEL could be identified for the tertiary monothiols or for sufficiently structurally related substances			
12.038 561	8-Mercapto-p-menthan-3-one		II
12.085 523	p-Menth-1-ene-8-thiol		II
12.137 544	3-Mercapto-3-methylbutan-1-ol		I
12.138 549	3-Mercapto-3-methylbutyl formate		I
12.145 548	4-Methoxy-2-methylbutane-2-thiol		I
12.252 1669	4-Mercapto-4-methyl-2-pentanol		I
12.259 1673	1-Mercapto-p-menthan-3-one		II

Table 2: The Subgrouping of the 44 Simple Aliphatic and Aromatic Sulfides and Thiols in FGE.91Rev2.

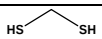
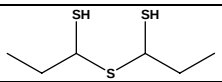
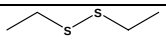
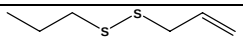
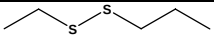
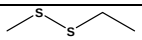
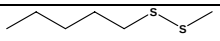
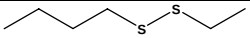
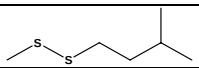
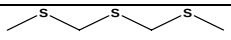
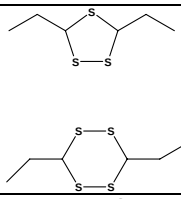
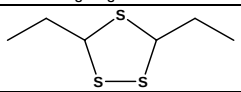
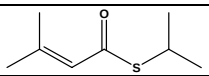
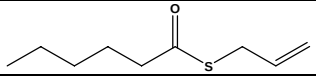
FL-no JECFA-no	EU Register name	Structural formula	Structural Class
IV Dithiols In FGE.08Rev5 this subgroup was represented by supporting substances [FL-no: 12.022, 12.034] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al., 1974b; Cox et al., 1974c).			
12.243 1661	Dimercaptomethane		I
12.284 1709	bis(1-Mercaptopropyl)sulfide		I
12.293 1660	Ethane-1,1-dithiol		I
V Acyclic and cyclic disulphides In FGE.08Rev5 this subgroup was represented by supporting substances [FL-no: 12.028, 12.068] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (Cox et al., 1974b; Gallo et al., 1976).			
12.012 1699	Diethyl disulfide		I
12.021 1700	Allyl propyl disulfide		II
12.126 1694	Ethyl propyl disulfide		I
12.153 1693	Methyl ethyl disulfide		I
12.253 1697	Amyl methyl disulfide		I
12.254 1698	Butyl ethyl disulfide		I
12.294 1696	Isopentyl methyl disulfide		I
VI Acyclic polysulphides The substances previously allocated to the group are no longer supported for use as flavouring substances in Europe by Industry.			
VII Mono-, di-, tri-, and poly-sulphides with thioacetal structure In FGE.08Rev5 this subgroup was represented by supporting substances [FL-no: 15.009; 15.025; 15.034; 15.036; 16.030] for which adequate toxicolgical studies were available. The lowest value not giving rise to adverse effects was considered a NOAEL (BIBRA, 1976; Mondino, 1981; Griffiths et al., 1979; Cox et al., 1973).			
12.240 1684	2,4,6-Trithiaheptane		I
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		II
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		II

Table 2: The Subgrouping of the 44 Simple Aliphatic and Aromatic Sulfides and Thiols in FGE.91Rev2.

FL-no JECFA-no	EU Register name	Structural formula	Structural Class
VIII Thioesters In FGE.08Rev5this subgroup was represented by supporting substances [FL-no: 12.018] for which an adequate NOAEL exists (Shellenberger, 1970).			
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		I
12.275 1681	Allylthio hexanoate		II
X Sulphoxides/sulphones and sulphonates The substances previously allocated to the group are no longer supported for use as flavouring substances in Europe by Industry			

The Panel agrees with JECFA that all candidate substances in this FGE can be evaluated through the Procedure.

For 10 of these substances the Panel did not agree with the way the JECFA carried out the evaluation.

Three substances, di-isopentyl thiomalate [FL-no: 12.108], benzyl methyl sulphide [FL-no: 12.077] and methyl phenyl sulphide [FL-no: 12.162]), have been cleared by JECFA at step B5 (the MSDI < 1.5 μg per person per day). This approach is not supported by the Panel (see section 2.1.2).

However, for [FL no: 12.108] which belongs to subgroup III, NOAELs ranging from 0.06 to 0.7 mg/kg bw/day are available based on adequate 90-day sub-chronic studies on the four supporting substances in subgroup III of FGE.08Rev5. These NOAELs have been reported for 3-mercapto-2-butanol [FL-no: 12.024], cyclopentanethiol [FL-no: 12.029], 2-,3- and 10-mercaptopinane [FL-no: 12.035] and 2,6-(dimethyl)-thiophenol [FL-no: 12.082] (Cox et al., 1974a; Morgareidge and Oser, 1970a; Oser, 1966; Peano et al., 1981). Using the lowest NOAEL of 0.06 mg/kg bw and an EU MSDI of 0.012 μg/*capita* a margin of safety of 3 x 10^5 can be calculated. The Panel considered this margin of safety sufficiently large to conclude no safety concern at the estimated level of intake at step B4 of the Procedure.

Because benzyl methyl sulphide and methyl phenyl sulphide [FL-no: 12.077 and 12.162] are sulphides the Panel has allocated them to subgroup I, despite the fact that there are no other sulphides with aromatic substituents in this subgroup. Thus, no structurally related substance occurs in this subgroup which can provide an adequate NOAEL to evaluate [FL-no: 12.077 and 12.162]. However, sulphides can be considered metabolites of thiols. For subgroup III (thiols), a common biotransformation pathway is methylation of the thiol to the corresponding sulphide followed by S-oxidation and elimination (FGE.08Rev5). Therefore, toxicity data of thiols can be used for the evaluation of sulphides assuming that the toxicity of thiols is higher than the toxicity of sulphides because of the greater reactivity of the thiol group as compared to the sulphide group. For the thiols in subgroup III, 90 days studies are available for four substances, including one with an aromatic ring (2,6-(dimethyl)thiophenol [FL-no: 12.082]). For this substance a NOAEL of 0.43 mg/kg bw/day was derived. Using this NOAEL of 0.43 mg/kg bw/day and the MSDIs of 0.09 μg/*capita*/day for benzyl methyl sulphide and of 0.012 μg/*capita*/day for methyl phenyl sulphide, respectively, margins of safety of 2.8 x 10^4 and 2.1 x 10^5, are derived. The Panel considered these margins of safety sufficiently large to conclude no safety concern at the estimated level of intake at step B4 of the Procedure.

For six of the seven tertiary thiols in the present FGE [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] the JECFA derived a NOAEL from a 90-day study on the secondary thiol, 2-mercapto-3-butanol [FL-no: 12.024] (Cox et al., 1974a). For [FL-no: 12.085] the JECFA has used a NOAEL derived from a 90-day study on the secondary thiol, cyclopentanethiol [FL-no: 12.029] (Morgareidge and Oser, 1970a).The Panel did not agree with the JECFA that the tertiary thiols are sufficiently structurally related to the secondary thiol substances used for deriving the NOAELs. Thus no NOAEL could be identified for the tertiary thiols or for sufficiently structurally related substances. Accordingly the Panel concluded at step B4 (contrary to the JECFA) that further data are required for the seven tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259].

For in total 37 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, , 12.264, 12.265, 12.267, 12.273, 12.274, 12.275, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297, 15.049 and 17.036] the Panel concluded in line with the JECFA: "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach at step B4 of the Procedure.

CONCLUSION

This consideration deals with 44 simple aliphatic and aromatic sulphides and thiols with and without an additional oxygenated functional group which are in the Register and which were evaluated by the JECFA at its 53rd and 68th meetings.

The Panel concluded that these 44 candidate substances are structurally related to the aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups evaluated by EFSA in the Flavouring Group Evaluation 08, Revision 5 (FGE.08Rev5). The 44 JECFA evaluated substances are distributed into six subgroups of structurally related substances. The subgrouping is the same as used in FGE.08Rev5.

This revision is made because additional genotoxicity data have become available for 4-mercapto-4-methyl-2-pentanone [FL-no: 12.169] from FGE.74Rev3, which is a representative for the group of tertiary monothiols and therefore covers the seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] in this FGE. In addition, data on production volume and specification were submitted.

Although the available data are limited the Panel considered that for the 44 substances in FGE.91Rev2 the genotoxicity data do not preclude evaluating these substances through the Procedure.

However, the Panel noted that candidate substance 3-(methylthio)heptenal [FL-no: 12.273] contains 5 to 7 % of an α,β -unsaturated aldehyde, (2-(E)-heptenal [FL-no: 05.150], for which a concern has been raised due to the presence of a structural alert for genotoxicity. This substance is a candidate flavouring substance which is under evaluation in FGE.200Rev1 (FGE.19 subgroup 1.1.1).

The Panel agrees with the JECFA that all substances can be evaluated through the Procedure. For 34 substances the conclusion was that they do not pose a safety concern when used as flavouring substance at their estimated intake based on the MSDI approach.

For 10 substances [FL-no: 12.038, 12.077, 12.085, 12.108, 12.137, 12.138, 12.145, 12.162, 12.252 and 12.259] the Panel did not agree with the application of the Procedure by the JECFA for the following reasons:

For the substances [FL-no: 12.077, 12.108 and 12.162], the JECFA has cleared by the JECFA at step B5 (the MSDI < 1.5 μg person per day). However, the Panel considers that adequate NOAELs exist to evaluate these substances and concluded at step B4 "No safety concern at the estimated levels of intake based on the MSDI approach".

For the tertiary thiols [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259], contrary to the JECFA, the Panel concluded that there are no adequate NOAELs for these candidate substances or from structurally related substances and that additional toxicity data are required to finalise the evaluation of these seven substances.

For 34 substances, use levels have been provided by the Industry. The mTAMDI figures for five substances [FL-no: 12.264, 12.284, 12.274, 12.108 and 12.139] are above the threshold of concern for their structural classes. For these substances more reliable data are needed. On the basis of such data the flavouring substances should be reconsidered using the Procedure. For 10 substances [FL-no: 12.038, 12.077, 12.085, 12.137, 12.138, 12.145, 12.162, 12.265, 12.267 and 17.036] for which use levels have not been provided, use levels are needed to calculate the mTAMDI values in order to identify those flavouring substances that need a more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 44 JECFA evaluated substances, for which the Panel concluded that they could be evaluated through the Procedure, can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria and identity are available for all 44 substances.

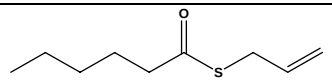
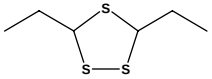
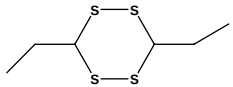
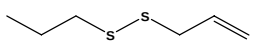
Thus, for seven substances [FL-no: 12.038, 12.085, 12.137, 12.138, 12.145, 12.252 and 12.259] evaluated through the Procedure, the Panel concluded that additional toxicity data are required.

For candidate substance 3-(methylthio)heptenal [FL-no: 12.273], which contains 5 to7 % of an α,β-unsaturated aldehyde, 2-(E)-heptenal, with a possible genotoxic potential, the Panel cannot conclude that the material of commerce for this candidate substance is not of safety concern, until either this component is cleared with respect to a concern for genotoxicity, or this component is removed from the commercial product.

For 36 substances [FL-no: 12.012, 12.017, 12.021, 12.077, 12.108, 12.126, 12.130, 12.134, 12.139, 12.146, 12.153, 12.162, 12.240, 12.242, 12.243, 12.253, 12.254, 12.264, 12.265, 12.26712.274, 12.275, 12.276, 12.284, 12.285, 12.286, 12.287, 12.288, 12.289, 12.290, 12.292, 12.293, 12.294, 12.297, 15.049 and 17.036] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.”.

SUMMARY OF GENOTOXICITY DATA

Table 3: Genotoxicity Data (*in vitro / in vivo*) evaluated by JECFA (JECFA, 2008a)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
12.275 1681	Allylthio hexanoate		Reverse Mutation	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	5[(a)], 15[(a)], 50, 150,500, 1500 or 5000 µg/plate	Negative[(b)]	(King and Harnasch, 2002)
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		Reverse Mutation[(c)]	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	0.1, 0.316, 1, 3, 16 or10 µg/plate	Negative[(b)]	(Uhde, 2005)
			Reverse Mutation	*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537	0.1, 0.316, 1, 3, 16 or10 µg/plate	Negative[(b)]	(Uhde, 2005)
							
12.021 1700	Allyl propyl disulfide		Reverse Mutation[(d)]	*S.typhimurium* TA97, TA98, TA100, TA102, TA1535, TA1537	Up to 333 µg/plate	Negative[(b)]	(Zeiger et al., 1988)
	Allyl propyl disulfide [(e)]		Reverse Mutation[(f)]	*S.typhimurium* TA100	Not specified	Negative[(b)]	(Eder et al., 1982b)
	Allyl propyl disulfide [(g)]		Reverse Mutation[(f)]	*S.typhimurium* TA100	0.0015 – 0.15 µl/ml 1.5 – 150 µg/ml	Negative[(b)]	(Eder et al., 1980)

(a): Concentration tested in the absence of metabolic activation.
(b): With and without metabolic activation.
(c): Plate incorporation method.
(d): Preincubation method.
(e): Mixture of 32 % allyl propyl disulfide, 31 % propyl disulfide and 32 % allyl disulfide.
(f): Liquid suspension method.
(g): Mixture of 31 % allyl propyl disulfide, 37 % propyl disulfide and 32 % allyl disulfide.
(h): Calculated based on specific gravity of allyl propyl disulfide (0.999 - 1.005 g/ml).
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Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.08Rev5 (EFSA CEF Panel, 2012)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
Subgroup I – Acyclic Sulphides						
(Diallyl sulphide [12.088])	Ames test	*S. typhimurium* TA100	0.004 – 0.44 µg/ml	Negative (±S9)	(Eder et al., 1982a)	Review. No details on method and results reported. Only TA100 used.
	Sister chromatid exchange	Chinese hamster ovary cells	200 - 600 µg/ml	Positive[(a)]	(Musk et al., 1997)	Limited quality of study. Insufficiently reported.
	Chromosomal aberrations	Chinese hamster ovary cells	200 - 600 µg/ml	Positive [(a)]	(Musk et al., 1997)	Limited quality of study. Insufficiently reported.
Di-(1-propenyl)-sulfid (mixture) [12.298]	*Ames test*	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537	1 – 100 µg/plate	Negative[(a)]	(Stien, 2005)	Un-published GLP study. Study considered valid.
Subgroup II – Cyclic Sulphides						
Tetrahydrothiophene [15.102]	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	50 – 5000 µg/plate	Negative (±S9)	(Pennwalt Corporation, 1987a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Cytogenetic assay	Human lymphocytes	12.5 – 125 µg/ml	Negative (±S9)	(Pennwalt Corporation, 1987a)	Validity of this study cannot be fully evaluated (only abstract provided).
	HPRT assay	Chinese hamster ovary cells	100 – 200 µg/ml	Negative (±S9)	(Pennwalt Corporation, 1987a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Sister chromatid exchange	Chinese hamster ovary cells	15.63 – 125 µg/ml	Negative (±S9)	(Pennwalt Corporation, 1987b)	Validity of this study cannot be fully evaluated (only abstract provided).
	Unscheduled DNA synthesis	Human epithelial cells	2.5 – 5120 µg/ml	Negative (±S9)	(Pennwalt Corporation, 1987a)	Validity of this study cannot be fully evaluated (only abstract provided).
(1,4-Dithiane [15.066])	Ames test	*S. typhimurium* TA98, TA100	0.8 – 100 µ mol/plate (96.2 - 12024 µg/plate)	Positive (-S9) Negative (+S9)	(Lee et al., 1994)	Only two strains were tested, otherwise acceptable study.
	Sister chromatid	Chinese hamster ovary cells	2000 µM (240 µg/ml)	Negative	(Lee et al., 1994)	Insufficient quality.

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.08Rev5 (EFSA CEF Panel, 2012)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
	exchange			(±S9)		
Subgroup III – Monothiols						
2-Methylpropane-2-thiol [12.174]	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10000 µg/plate	Negative (±S9)	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Forward mutational MLTK assay	L5178Y/tk+/- mouse lymphoma cells	1000 µg/ml	Positive (-S9) Negative (+S9)	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
	Sister chromatid exchange	Chinese hamster ovary cells	1350 µg/ml	Negative (+S9) [(b)]	(Phillips Petroleum Company, 1990a)	Validity of this study cannot be fully evaluated (only abstract provided).
(Allyl mercaptan [12.004])	Modified Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.005 – 1.5 µl/ml (4.6 – 1400 µg/ml)	Negative (±S9)	(Eder et al., 1980)	Acceptable quality.
(Benzyl mercaptan [12.005])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
(2-Mercaptopropionic acid [12.039])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
(Benzenethiol [12.080])	Ames test	*S. typhimurium* TA98, TA100	25 – 500 µg/plate	Negative (±S9)	(LaVoie et al., 1979)	Insufficient quality (only two strains were used, and all doses -except the lowest dose - were toxic).
Subgroup IV – Dithiols						
(1,2-Ethanedithiol [12.066])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 doses up to 5000 µg/plate	Negative (±S9)	(Phillips Petroleum Company, 1990b)	Validity cannot be fully evaluated (only abstract provided).
	Sister chromatid exchange	Chinese hamster ovary cells	0.5 - 50 µg/ml	Positive (±S9)	(Pence et al., 1982)	Acceptable quality.
	Forward mutational assay	L5178Y/tk+/- mouse lymphoma cells	150 µg/ml	Positive (-S9)	(Pence et al., 1982)	Positive only at cytotoxic concentrations.
	Forward mutational	L5178Y/tk+/- mouse lymphoma	1 µg/ml	Negative	(Pence et al., 1982)	Insufficiently

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.08Rev5 (EFSA CEF Panel, 2012)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
	assay	cells		(+S9)		documented.
Subgroup V – Acyclic Di-, Tri-, and Poly-sulphides						
(Diallyl disulphide [12.008])	Modified Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.0015 – 0.15 µg/ml	Negative (±S9)	(Eder et al., 1980)	Acceptable quality.
	Sister chromatid exchange	Chinese hamster ovary cells	2 - 25 µg/ml	Weakly positive (±S9)	(Musk et al., 1997)	Limited quality. Insufficiently reported.
	Chromosomal aberrations	Chinese hamster ovary cells	2 - 25 µg/ml	Positive (±S9)	(Musk et al., 1997)	Limited quality. Insufficiently reported.
(Dimethyl disulphide [12.026])	Ames test	*S. typhimurium* TA98, TA100, TA102	0.000011 – 1.1 mmol/plate (1.04 - 104000 µg/plate)	Negative (±S9)	(Aeschbacher et al., 1989)	Limited quality (only 3 strains used).
(Phenyl disulphide [12.043])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
(Benzyl disulphide [12.081])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative (±S9)	(Wild et al., 1983)	Review. Methods and results insufficiently documented.
Dibutyl disulphide [12.111]	Forward mutational assay	Mouse lymphoma cells	NR	Negative (-S9)	(Dooley et al., 1987)	Validity cannot be fully evaluated (only abstract provided).
Subgroup VIII – Thioesters						
(Methylthio 2-(acetyloxy)propionate [12.203])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. Coli* WP2uvrA	0.156-5.0 mg/plate (156-5000 µg/plate	Negative (±S9)	(Watanabe and Morimoto, 1989a)	Acceptable quality.
(Methylthio 2-(propionyloxy) propionate [12.227])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. Coli* WP2uvrA	0.156 – 5.0 mg/plate (156 - 5000 µg/plate)	Negative (±S9)	(Watanabe and Morimoto, 1989b)	Acceptable quality.
(Methylsulfinyl methane [12.175]) (synonym: dimethylsulfoxid, DMSO)	Ames test	*S. typhimurium* TA97, TA98, TA100	100000 – 300000 µg/plate	Negative (±S9)	(Brams et al., 1987)	Insufficient method (3 strains and 3 concentrations only).
	Ames test	*S. typhimurium* TA97, TA98, TA100, TA1535, TA1537	100 – 10000 µg/plate	Negative (±S9)	(Zeiger et al., 1992)	Acceptable quality.
	Ames test	*S. typhimurium* TA97, TA98,	0.1 – 0.4 ml/plate (100000 -	Negative	(Hakura et al.,	Good quality study.

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.08Rev5 (EFSA CEF Panel, 2012)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
		TA100, TA102, TA104, TA1535, TA1538, *E. Coli* WP2	400000 µg/plate)	(-S9)	1993)	
	Ames test	*S. typhimurium* TA1537, TA2637, *E. Coli* WP2uvrA	0.1 – 0.4 ml/plate (100000 - 400000 µg/plate)	Positive (-S9) [(e)]	(Hakura et al., 1993)	Good quality study. Positive at high doses with reduced bacterial survival. Doses routinely used in Ames test were negative.

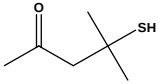
NR: Not reported.
(a): With and without metabolic activation at clearly cytotoxic concentrations.
(b): A statistically significant increase in the number of SCEs per chromosome was seen at 1350 µg/ml and the 450 µg/ml dose level in the presence of metabolic activation; but no significant increase was seen in the remaining dose levels, and no dose level showed a two fold increase in SCEs; therefore, t-butyl mercaptan is not considered to be mutagenic.
(c): With 100 µl/plate fecalase.
(d): With 100 µl/plate S9 metabolic activation and 100 µl/plate fecalase. Negative results reported after 2 days of incubation. Results for TA98 test strain were positive after 5 days of incubation.
(e): Positive results obtained at doses where lethal toxicity was observed. Negative results obtained at doses routinely used in Ames test.
(f): Thiosulfonates in general and methyl methane thiosulfonate in particular, are non-specific antimicrobial agents that are active at low concentrations on prokaryotic bacteria, as well as on yeast and other eukaryotic fungi. This was even pointed out by Dorange et al. (1983). Therefore bacterial test systems and yeast assays are not appropriate to evaluate genotoxicity of thiosulfonates.

Table 5: Genotoxicity Data (*in vivo*) EFSA / FGE.08Rev5 (EFSA CEF Panel, 2012)

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
Subgroup I – Acyclic Sulphides							
(Diallyl sulphide [12.088])	*In vivo* mouse micronucleus test	Mouse	Gavage	0.33 – 0.67 mM/kg (38 – 77 mg/kg)[(a)]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup III – Monothiols							
(2-Mercaptopropionic acid [12.039])	*In vivo* Basc test	*Drosophila*	Dietary route	10 mM (1061 µg/ml)	Negative	(Wild et al., 1983)	Limited quality (insufficiently documented). The article compiles results obtained with 76 substances in 3 test systems.
Subgroup V – Acyclic and cyclic Disulphides							
(Allyl disulphide [12.008])	*In vivo* mouse micronucleus test	Mouse	Gavage	0.33 – 0.67 mM/kg (48 – 98 mg/kg) [(a)]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup VI – Acyclic Tri- and Polysulphides							
(Diallyl trisulphide [12.009])	*In vivo* mouse micronucleus test	Mouse	Gavage	0.33 – 0.67 mM/kg (59 - 120 mg/kg) [(a)]	Negative	(Marks et al., 1992)	Insufficient quality. Mixture of three substances was tested.
Subgroup X – Sulphoxides/Sulphones and Sulphonates							
Methyl methane-thiosulfonate [12.159]	*In vivo* genetic mutation	*Nicotiana tabacum* seeds	-	2 - 4 mg/ml (2000 - 4000 µg/ml)	Negative	(Dorange et al., 1983)	Obscure test system[(b)]. This assay cannot be regarded as standard test.
	In vivo genetic mutation	*Nicotiana tabacum* seeds	-	50 – 400 µg/ml	Negative	(Dorange et al., 1983)	Obscure test system[(b)]. This assay cannot be regarded as standard test.

(a): Study used a mixture of allyl sulfide, allyl disulfide and ally trisulfide in the respective ratio, 68:20:12.
(b): Heterozygotic seeds were used. After exposure, the seeds were blotted on filter paper and planted in earthenware pots in medium normally used for planting tobacco. The leaves were analysed for alterations indicating genotoxicity.

Table 6: Summary of Additional Genotoxicity Data on 2-methyl-4-oxopentane-2-thiol

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference	Comments
12.169	2-Methyl-4-oxopentane-2-thiol		Reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537 and TA102	5, 15. 81, 50, 158.1, 500, 1581 and 5000 µg/plate[(a)]	Negative	(Mc Garry, 2012)	Valid GLP study, in compliance with OECD 471 Guideline
					156.3, 312.5, 625.0, 1250, 2500 and 5000 µg /plate[(a,b)]	Negative		

(a): In the absence and presence of S9-mix metabolic bioactivation.
(b): Assay modified with pre-incubation in presence of S9-mix.

SUMMARY OF SAFETY EVALUATIONS

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

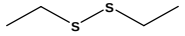
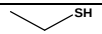
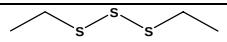
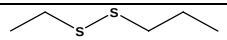
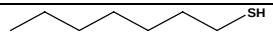
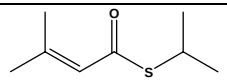
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.012 1699	Diethyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.017 1659	Ethanethiol		0.49 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.114 1701	Diethyl trisulfide		16 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required. No longer supported by Industry (DG SANCO, 2013b).	
12.126 1694	Ethyl propyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.130 1663	Heptane-1-thiol		0.037 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.134 1679	S-Isopropyl 3-methylbut-2-enethioate		0.012 ND	Class I B3: Intake below threshold	d	No safety concern at the estimated level of intake based on the	No safety concern at the estimated level of intake based on the

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

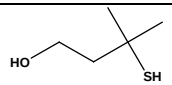
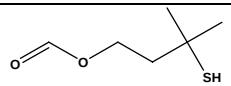
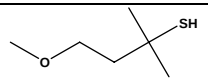
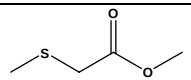
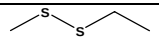
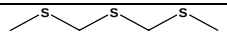
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
				B4: Adequate NOAEL exists		MSDI approach.	MSDI approach.
12.137 544	3-Mercapto-3-methylbutan-1-ol		8.6 2	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	
12.138 549	3-Mercapto-3-methylbutyl formate		0.13 0.1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	
12.145 548	4-Methoxy-2-methylbutane-2-thiol		0.14 0.8	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	
12.146 1691	Methyl (methylthio)acetate		0.24 1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.153 1693	Methyl ethyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.240 1684	2,4,6-Trithiaheptane		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

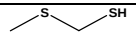
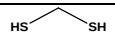
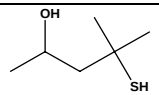
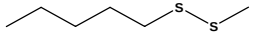
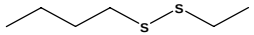
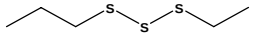
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.242 1675	Methylthiomethylmercaptan		0.012 0.1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.243 1661	Dimercaptomethane		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.252 1669	4-Mercapto-4-methyl-2-pentanol		0.012 0.1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	
12.253 1697	Amyl methyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.254 1698	Butyl ethyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.256 1695	Ethyl propyl trisulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required. No longer supported by Industry (DG SANCO, 2013b).	

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

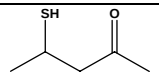
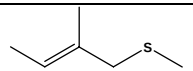
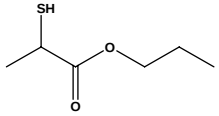
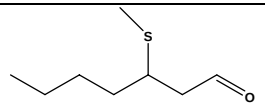
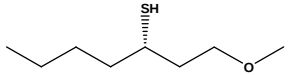
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.264 1670	4,2-Thiopentanone		0.12 0.07	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.265 1683	2-Methyl-1-methylthio-2-butene		0.012 0.1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.267 1667	Propyl-2-mercaptopropionate		0.012 0.1	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.273 1692	3-(Methyl thio)heptanal		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	Secondary component 2-(E)-heptenal (5-7 %) correpond to [FL-no: 05.150] which is under evaluation in FGE.200Rev1: additional genotoxicity data required.	Register name to be changed to 3-(Methyl thio)heptanal. Secondary component 2-(E)-heptenal (5-7 %) correpond to [FL-no: 05.150] which is under evaluation in FGE.200Rev1: additional genotoxicity data required.
12.276 1671	(S)-1-Methoxy-3-heptanethiol		0.012 2	Class I B3: Intake below threshold B4: Adequate	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

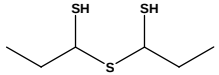
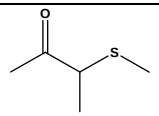
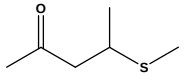
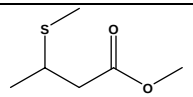
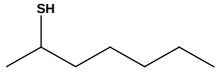
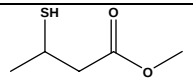
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
				NOAEL exists			
12.284 1709	bis(1-Mercaptopropyl)sulphide		0.12 0.6	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.285 1688	3-Methylthio-2-butanone		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.286 1689	4-Methylthio-2-pentanone		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.287 1690	Methyl 3-(methylthio)butanoate		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.288 1664	Heptan-2-thiol		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.290 1674	Methyl-3-mercaptobutanoate		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

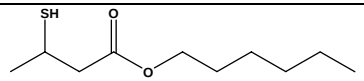
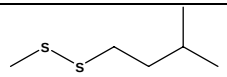
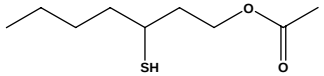
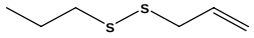
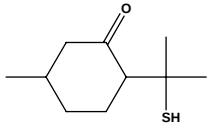
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.292 1704	Hexyl 3-mercaptobutanoate		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.293 1660	Ethane-1,1-dithiol		0.012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.294 1696	Isopentyl methyl disulfide		0.012 ND	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.297 1708	3-Mercaptoheptyl acetate		0.0012 0.01	Class I B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.021 1700	Allyl propyl disulfide		0.037 ND	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.038 561	8-Mercapto-p-menthan-3-one		24 2	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

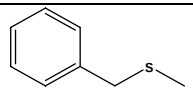
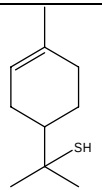
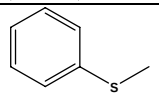
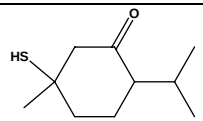
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.077 460	Benzyl methyl sulfide		0.09 0.02	Class II B3: Intake below threshold B4: No adequate NOAEL B5: Intake below 1.5 µg/person/day	f	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.085 523	p-Menth-1-ene-8-thiol		23 1	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	
12.162 459	Methyl phenyl sulfide		0.012 0.4	Class II B3: Intake below threshold B4: No adequate NOAEL B5: Intake below 1.5 µg/person/day	f	No safety concern at the estimated level of intake based on the MSDI.	No safety concern at the estimated level of intake based on the MSDI.
12.259 1673	1-Mercapto-p-menthan-3-one		0.24 ND	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	Toxicity data required.	

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

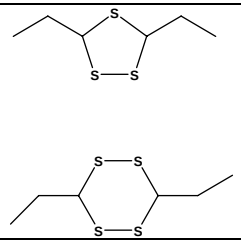
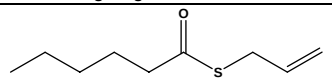
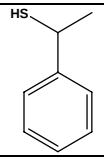
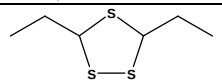
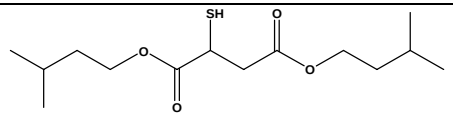
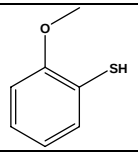
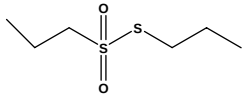
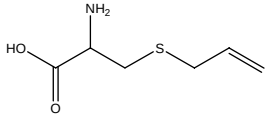
FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.274 1687	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides		0.61 ND	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.275 1681	Allylthio hexanoate		0.012 ND	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.289 1665	1-Phenylethylmercaptan		0.012 ND	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
15.049 1686	3,5-Diethyl-1,2,4-trithiolane		0.61 0.01	Class II B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.108 1672	Di-isopentyl thiomalate		0.012 ND	Class III B3: Intake below threshold, B4: No adequate NOAEL B5: Intake below 1.5 µg/person/day	f	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 7: Summary of Safety Evaluation by the JECFA (JECFA, 2000; JECFA, 2008a)

FL-no JECFA -no	EU Register name	Structural formula	EU MSDI [(a)] US MSDI (µg/*capita*/day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
12.139 1666	2-Mercaptoanisole		1.5 ND	Class III B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
12.272 1702	Propyl propanethiosulfonate		0.012 ND	Class III B3: Intake below threshold B4: No adequate NOAEL	Additional data required	Genotoxicity data required. No longer supported by Industry (DG SANCO, 2013b).	
17.036 1710	S-allyl-L-cysteine		30 2	Class III B3: Intake below threshold B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

(a): EU MSDI: Amount added to food as flavour in (kg / year) x 10^9 / (0.1 x population in Europe (= 375 x 10^6) x 0.6 x 365) = µg/*capita*/day.
(b): Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
(c): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(d): No safety concern based on intake calculated by the MSDI approach of the named compound.
(e): Data must be available on the substance or closely related substances to perform a safety evaluation.
(f): Cleared by JECFA as intake below 1.5 µg/person/day.
ND not determined

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

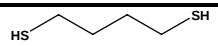
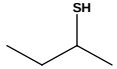
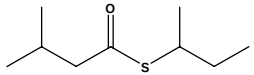
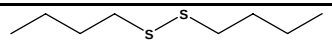
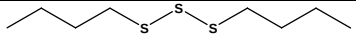
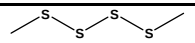
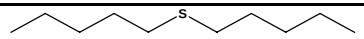
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
12.103	Butane-1,4-dithiol		0.3	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.104	Butane-2-thiol		0.18	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.106	S-2-Butyl 3-methylbutanethioate		0.8	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.111	Dibutyl disulfide		0.37	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.112	Dibutyl trisulfide		0.12	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.116	Dimethyl tetrasulfide		0.016	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.117	Dipentyl sulfide		0.0037	Class I B3: Intake below threshold,	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

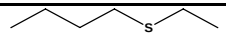
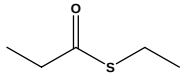
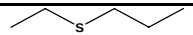
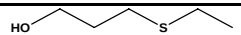
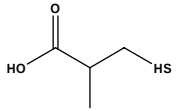
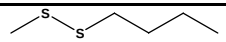
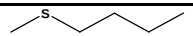
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
				B4: Adequate NOAEL exists			
12.124	Ethyl butyl sulfide		0.037	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.125	Ethyl propanethioate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.127	Ethyl propyl sulfide		0.085	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.129	3-(Ethylthio)propan-1-ol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.135	3-Mercapto-2-methylpropionic acid		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.151	Methyl butyl disulfide		0.0061	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.152	Methyl butyl sulfide		0.0024	Class I B3: Intake below threshold,	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

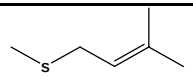
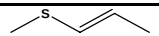
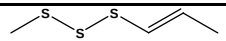
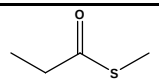
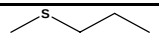
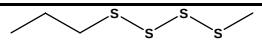
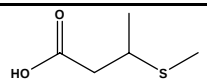
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
				B4: Adequate NOAEL exists			
12.158	Methyl isoprenyl sulfide		0.0012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.163	Methyl prop-1-enyl sulfide		0.0097	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.164	Methyl prop-1-enyl trisulfide		0.0061	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.165	S-Methyl propanethioate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.166	Methyl propyl sulfide		0.0024	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.167	Methyl propyl tetrasulfide		0.0037	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.178	3-(Methylthio)butyric acid		0.12	Class I B3: Intake below threshold,	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

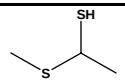
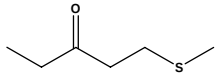
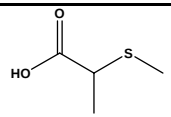
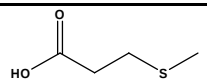
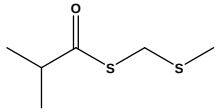
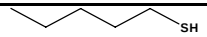
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
				B4: Adequate NOAEL exists			
12.180	1-(Methylthio)ethane-1-thiol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.181	1-(Methylthio)pentan-3-one		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.182	2-(Methylthio)propionic acid		0.011	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.183	3-(Methylthio)propionic acid		0.21	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.189	S-(Methylthiomethyl) 2-methylpropanethioate		0.061	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.191	Pentane-1-thiol		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

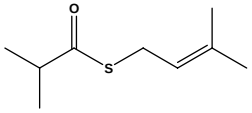
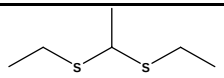
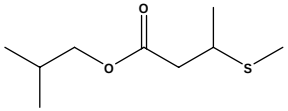
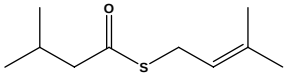
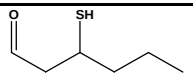
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
12.196	S-Prenyl thioisobutyrate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.199	Ethanethioic acid		0.0012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.200	1,1-bis(Ethylthio)-ethane		0.0012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.205	Mercaptoacetaldehyde		0.011	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.214	Isobutyl-3-(methylthio)butyrate		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.221	S-Prenyl thioisopentanoate		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.250	3-Mercaptohexanal		0.012	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

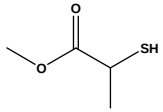
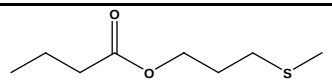
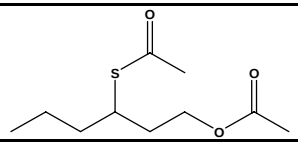
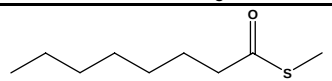
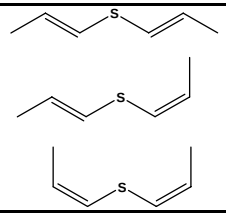
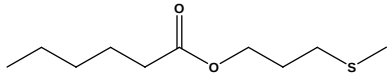
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
12.266	Methyl-2-mercaptopropionate		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	h	
12.277	3-(Methylthio)propyl butyrate		6.1	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.278	3-Acetyl-mercaptohexyl acetate		1.2	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.282	(S)-Methyl octanethioate		0.24	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	g	
12.298	Di-(1-propenyl)-sulfid (mixture)		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.299	3-(Methylthio)propyl hexanoate		0.061	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

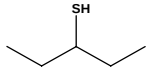
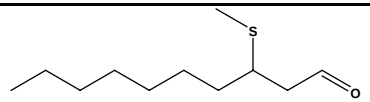
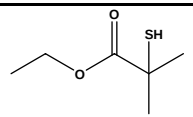
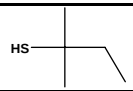
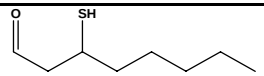
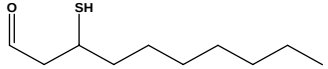
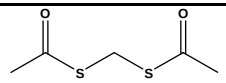
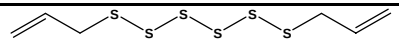
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
12.303	3-Pentanethiol		0.03	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.306	3-(Methylthio)-decanal		0.12	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.304	Ethyl-2-mercapto-2-methyl propanoate		0.012	Class I No evaluation			Pending update, as new genotoxicity data have become available.
12.172	2-Methylbutane-2-thiol		0.15	Class I No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
12.174	2-Methylpropane-2-thiol		0.0012	Class I No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
12.268	3-Mercaptooctanal			Class I No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
12.269	3-Mercaptodecanal			Class I No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
12.271	Methanedithiol diacetate			Class I No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
12.093	Diallyl hexasulfide		0.011	Class II B3: Intake below threshold, B4: No adequate	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

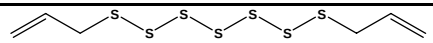
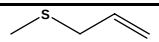
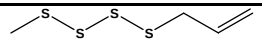
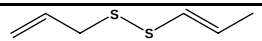
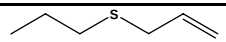
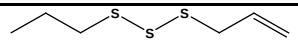
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
				NOAEL			
12.094	Diallyl heptasulfide		0.011	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.096	Allyl methyl sulfide		0.99	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.097	Allyl methyl tetrasulfide		0.012	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.098	Allyl prop-1-enyl disulfide		0.17	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.099	Allyl propyl sulfide		1.6	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.100	Allyl propyl trisulfide		0.12	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

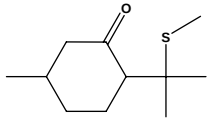
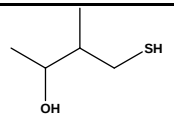
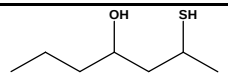
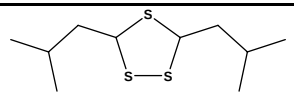
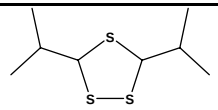
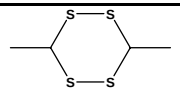
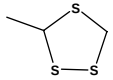
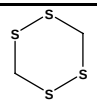
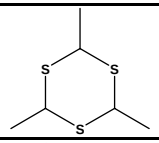
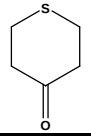
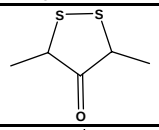
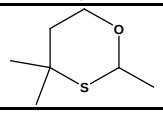
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
12.177	8-(Methylthio)-p-menthan-3-one		0.37	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.302	2-Butanol, 4-mercapto-3-methyl		0.061	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.305	2-Mercapto-4-heptanol		0.12	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.047	3,5-Di-isobutyl-1,2,4-trithiolane		0.024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.048	3,5-Di-isopropyl-1,2,4-trithiolane		0.0061	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.056	3,6-Dimethyl-1,2,4,5-tetrathiane		0.0024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.083	3-Methyl-1,2,4-trithiolane		0.0024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 8: Summary of Safety Evaluation by the EFSA (FGE.08Rev5) (EFSA CEF Panel, 2012)

FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
15.102	Tetrahydrothiophene		0.024	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
15.103	1,2,4,5-Tetrathiane		0.073	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.110	2,4,6-Trimethyl-1,3,5-trithiane		0.0061	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.111	1,2,4-Trithiolane		2.4	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.125	4-Tetrahydrothio-pyranone		0.12	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		Substance no longer supported by Industry (DG SANCO, 2012).
12.295	3,5-Dimethyl-1,2-dithiolane-4-one			Class II No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).
16.057	2,4,4-Trimethyl-1,3-oxathiane		0.0012	Class II No evaluation			Substance no longer supported by Industry (DG SANCO, 2012).

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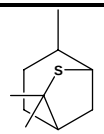
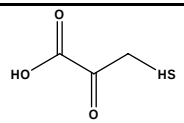
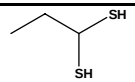
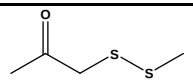
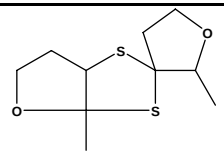
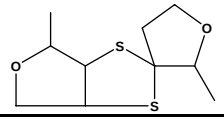
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
12.120	2,8-Epithio-p-menthane		3.7	Class III B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		No longer supported by Industry (DG SANCO, 2013b).
12.136	3-Mercapto-2-oxopropionic acid		0.24	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.300	1,1-Propanedithiol		0.12	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.301	Methyl-2-oxo-propyl disulfide		0.061	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.007	Spiro(2,4-dithia-1-methyl-8-oxabicyclo[3.3.0]octane -3,3'-(1'-oxa-2'-methyl)-cyclopentane) and Spiro(2,4-dithia-6-methyl-7-oxabicyclo[3.3.0]octane -3,3'-(1'-oxa-2'-methyl)-cyclopentane)	 **I**  **II**	6.1	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

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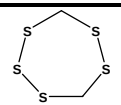
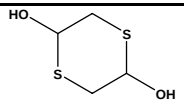
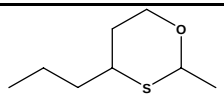
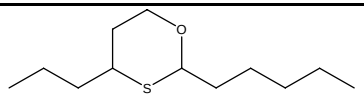
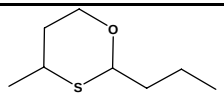
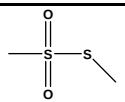
FL-no	EU Register name	Structural formula	MSDI [(a)] (µg/capita/ day)	Class [(b)] Evaluation procedure path [(c)]	Outcome on the named compound [[(d)] or [(e)]]	Outcome on the material of commerce [[(f)], [(g)] or [(h)]]	Evaluation remarks
15.081	Lenthionine		0.012	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
15.134	2,5-Dihydroxy-1,4-dithiane		6.1	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
16.062	trans-2-Methyl-4-propyl-1,3-oxathiane		1.0	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
16.114	2-Pentyl-4-propyl-1,3-oxathiane		0.12	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
16.122	4-Methyl, 2-propyl, 1-3-oxathiane		0.24	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
12.159	Methyl methanethiosulfonate		0.061	Class III No evaluation			No longer supported by Industry (DG SANCO, 2013b).

(a): EU MSDI: Amount added to food as flavour in (kg / year) x 10^9 / (0.1 x population in Europe (= 375 x 10^6) x 0.6 x 365) = µg/*capita*/day.
(b): Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
(c): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(d): No safety concern based on intake calculated by the MSDI approach of the named compound.
(e): Data must be available on the substance or closely related substances to perform a safety evaluation.
(f): No safety concern at the estimated level of intake of the material of commerce meeting the specification requirement (based on intake calculated by the MSDI approach).

(g): 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.
(h): No conclusion can be drawn due to lack of information on the purity of the material of commerce.

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APPENDIX A: USE LEVELS AND mTAMDI

Normal and maximum use levels provided by the Flavour Industry (EFFA, 2004; EFFA, 2006; Flavour Industry, 2004; Flavour Industry, 2005; Flavour Industry, 2006; Flavour Industry, 2007a) in accordance with the Commission Regulation (EC) No 1565/2000 (EC, 2000).

The normal and maximum use levels are shown in Table A.1. Based on these normal use levels mTAMDI figures can be calculated (see Table A.2).

Table A.1: Normal and Maximum use levels (mg/kg) available for JECFA evaluated Substances in FGE.91Rev2

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**
12.012	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.017	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.021	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.108	0.4 2	0.2 1	0.4 2	0.3 1.5	- -	0.4 2	0.2 1	0.4 2	0.1 0.4	0.1 0.4	- -	- -	0.2 1	0.4 2	0.2 1	0.4 2	1 5	0.2 1
12.114	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.3	0.2 1	0.4 2	0.1 0.5
12.126	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.3	0.2 1	0.4 2	0.1 0.5
12.130	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.134	0.4 2	0.2 1	0.4 2	0.3 1.5	- -	0.4 2	0.2 1	0.4 2	0.1 0.4	0.1 0.4	- -	- -	0.2 1	0.4 2	0.2 1	0.4 2	1 5	2 1
12.139	0.4 2	0.2 1	0.4 2	0.3 1.5	- -	0.4 2	0.2 1	0.4 2	0.1 0.4	0.1 0.4	- -	- -	0.2 1	0.4 2	0.2 1	0.4 2	1 5	0.2 1
12.146	0.4 2	0.2 1	0.4 2	0.3 1.5	- -	0.4 2	0.2 1	0.4 2	0.1 0.4	0.1 0.4	- -	- -	0.2 1	0.4 2	0.2 1	0.4 2	1 5	0.2 1
12.153	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.3	0.2 1	0.4 2	0.1 0.5
12.240	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.242	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.5	0.2 1	0.4 2	0.1 0.5
12.243	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1

Table A.1: Normal and Maximum use levels (mg/kg) available for JECFA evaluated Substances in FGE.91Rev2

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**
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.252	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.253	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.254	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.256	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.259	0.2	0.1	0.2	0.2	-	0.2	0.1	0.2	0.1	0.1	-	-	0.1	0.2	0.1	0.2	0.4	0.1
	1	0.5	1	1	-	1	0.5	1	0.2	0.2	-	-	0.5	1	0.5	1	2	0.5
12.264	5	5	-	2	2	-	-	10	3	-	-	-	5	-	1	5	5	-
	10	20	-	10	10	-	-	30	20	-	-	-	30	-	5	10	30	-
12.273	1	0.1	-	2	2	-	-	10	3	-	-	-	2	-	1	1	5	-
	10	1	-	10	10	-	-	50	20	-	-	-	10	-	10	10	30	-
12.274	10	5	-	5	5	-	-	10	10	-	-	-	10	-	1	5	10	-
	30	20	-	20	20	-	-	30	20	-	-	-	30	-	5	10	20	-
12.275	0.4	0.4	-	0.2	0.2	2	-	2.5	0.3	0.3	-	-	0.5	-	0.05	0.25	0.5	-
	2	2	-	10	10	10	-	12.5	1.5	1.5	-	-	5	-	0.5	1.3	2.5	-
12.276	0.001	0.01	0.001	0.001	-	0.001	0.002	0.002	0.002	0.002	-	-	0.003	0.003	0.001	0.005	0.001	0.001
	0.01	0.1	0.01	0.01	-	0.01	0.02	0.02	0.02	0.02	-	-	0.03	0.03	0.005	0.05	0.01	0.01
12.284	0.05	0.05	0.5	0.05	0.05	5	1	0.5	0.05	0.05	-	-	0.05	-	5	5	0.05	0.05
	1.25	1.25	12.5	1.25	1.25	125	25	12.5	1.25	1.25	-	-	1.25	-	125	125	1.25	1.25
12.285	1	-	0.5	-	-	-	-	0.8	0.2	-	-	-	1	-	0.5	-	-	-
	5	-	0.7	-	-	-	-	1	0.5	-	-	-	5	-	6	-	-	-
12.286	0.5	-	0.5	-	-	-	-	0.8	2	-	-	-	-	-	0.5	-	-	0.5
	0.7	-	0.7	-	-	-	-	1	0.5	-	-	-	-	-	0.6	-	-	1
12.287	0.01	0.001	0.01	0.05	-	-	-	-	0.05	-	0.001	-	0.05	-	0.001	-	0.05	0.05
	10	10	10	10	-	-	-	-	10	-	10	-	10	-	5	-	10	10
12.288	-	-	-	-	-	-	-	-	1	-	-	-	1	-	4	-	-	-
	-	-	-	-	-	-	-	-	5	-	-	-	5	-	10	-	-	-
12.289	0.001	-	-	0.001	-	0.002	-	0.002	0.002	-	-	-	0.005	-	0.001	0.002	-	0.1
	0.008	-	-	0.008	-	0.025	-	0.04	0.025	-	-	-	1	-	0.02	0.025	-	0.5
12.290	-	-	-	-	-	-	-	-	1	-	-	-	1	-	0.5	-	-	-
	-	-	-	-	-	-	-	-	5	-	-	-	5	-	5	-	-	-

Table A.1: Normal and Maximum use levels (mg/kg) available for JECFA evaluated Substances in FGE.91Rev2

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**
12.292	- -	- -	- -	- -	- -	- -	- -	- -	1 5	- -	- -	- -	1 5	- -	0.5 5	- -	- -	- -
12.293	- -	0.2 2	- -	0.2 2	- -	- -	- -	- -	1 5	- -	- -	- -	0.6 5	- -	0.2 2	- -	1 5	- -
12.294	- -	- -	0.25 0.5	- -	- -	- -	- -	0.25 0.5	1 1.5	- -	- -	- -	- -	- -	0.5 1	- -	- -	0.25 0.5
12.297	0.01 0.1	0.1 1	0.01 0.1	0.01 0.1	- -	0.01 0.1	0.02 0.2	0.02 0.2	0.02 0.2	0.02 0.2	- -	- -	0.03 0.3	0.03 0.3	0.01 0.05	0.05 0.5	0.01 0.1	0.01 0.1
15.049	0.2 1	0.1 0.5	0.2 1	0.2 1	- -	0.2 1	0.1 0.5	0.2 1	0.1 0.2	0.1 0.2	- -	- -	0.1 0.5	0.2 1	0.1 0.3	0.2 1	0.4 2	0.1 0.5

Table A.2: Estimated intakes based on the MSDI- and the mTAMDI approach – FGE.91Rev2

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
12.012	Diethyl disulfide	0.012	ND	78	Class I	1800
12.017	Ethanethiol	0.49	ND	78	Class I	1800
12.114	Diethyl trisulfide	16	ND	78	Class I	1800
12.126	Ethyl propyl disulfide	0.012	ND	78	Class I	1800
12.130	Heptane-1-thiol	0.037	ND	78	Class I	1800
12.134	S-Isopropyl 3-methylbut-2-enethioate	0.012	ND	370	Class I	1800
12.137	3-Mercapto-3-methylbutan-1-ol	8.6	2	ND	Class I	1800
12.138	3-Mercapto-3-methylbutyl formate	0.13	0.1	ND	Class I	1800
12.145	4-Methoxy-2-methylbutane-2-thiol	0.14	0.8	ND	Class I	1800

Table A.2: Estimated intakes based on the MSDI- and the mTAMDI approach – FGE.91Rev2

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
12.146	Methyl (methylthio)acetate	0.24	1	160	Class I	1800
12.153	Methyl ethyl disulfide	0.012	ND	78	Class I	1800
12.240	2,4,6-Trithiaheptane	0.012	ND	78	Class I	1800
12.242	Methylthiomethylmercaptan	0.012	0.1	78	Class I	1800
12.243	Dimercaptomethane	0.012	ND	78	Class I	1800
12.252	4-Mercapto-4-methyl-2-pentanol	0.012	0.1	78	Class I	1800
12.253	Amyl methyl disulfide	0.012	ND	78	Class I	1800
12.254	Butyl ethyl disulfide	0.012	ND	78	Class I	1800
12.256	Ethyl propyl trisulfide	0.012	ND	78	Class I	1800
12.264	4,2-Thiopentanone	0.12	0.07	2000	Class I	1800
12.265	2-Methyl-1-methylthio-2-butene	0.012	0.1	ND	Class I	1800
12.267	Propyl-2-mercaptopropionate	0.012	0.1	ND	Class I	1800
12.273	3-(Methyl thio)heptanal	0.012	ND	1800	Class I	1800
12.276	(S)-1-Methoxy-3-heptanethiol	0.012	2	1.9	Class I	1800
12.284	bis(1-Mercaptopropyl)sulphide	0.12	0.6	2000	Class I	1800
12.285	3-Methylthio-2-butanone	0.012	ND	320	Class I	1800
12.286	4-Methylthio-2-pentanone	0.012	0.01	430	Class I	1800
12.287	Methyl 3-(methylthio)butanoate	0.012	0.01	9	Class I	1800
12.288	Heptan-2-thiol	0.012	0.01	1400	Class I	1800
12.290	Methyl-3-mercaptobutanoate	0.012	0.01	320	Class I	1800
12.292	Hexyl 3-mercaptobutanoate	0.012	0.01	320	Class I	1800
12.293	Ethane-1,1-dithiol	0.012	0.01	230	Class I	1800
12.294	Isopentyl methyl disulfide	0.012	ND	300	Class I	1800

Table A.2: Estimated intakes based on the MSDI- and the mTAMDI approach – FGE.91Rev2

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
12.297	3-Mercaptoheptyl acetate	0.0012	0.01	19	Class I	1800
12.021	Allyl propyl disulfide	0.037	ND	78	Class II	540
12.038	8-Mercapto-p-menthan-3-one	24	2	ND	Class II	540
12.077	Benzyl methyl sulfide	0.09	0.02	ND	Class II	540
12.085	p-Menth-1-ene-8-thiol	23	1	ND	Class II	540
12.162	Methyl phenyl sulfide	0.012	0.4	ND	Class II	540
12.259	1-Mercapto-p-menthan-3-one	0.24	ND	78	Class II	540
12.274	3,6-Diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane mix in vegetable oil triglycerides	0.61	ND	2200	Class II	540
12.275	Allylthio hexanoate	0.012	ND	430	Class II	540
12.289	1-Phenylethylmercaptan	0.012	ND	14	Class II	540
15.049	3,5-Diethyl-1,2,4-trithiolane	0.61	0.01	78	Class II	540
12.108	Di-isopentyl thiomalate	0.012	ND	160	Class III	90
12.139	2-Mercaptoanisole	1.5	ND	160	Class III	90
12.272	Propyl propanethiosulfonate	0.012	ND	ND	Class III	90
17.036	S-allyl-L-cysteine	30	2	ND	Class III	90

ND: No intake data available

ABBREVIATIONS

BW	Body Weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DNA	Deoxyribonucleic acid
EFFA	European Flavour and Fragrance Association
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
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)
GLP	Good Laboratory Practice
HPRT	Hypoxanthine Phosphoribosyl transferase
ID	Identity
IP	Intraperitoneal
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MNBN	Micronucleated Binucleate cells
MS	Mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NCE	Normochromatic erythrocyte
No	Number
NOAEL	No Observed Adverse Effect Level

NMR	Nuclear Magnetic Resonance
NTP	National Toxicology Program
PCE	Polychromatic erythrocyte
RI	Replication Index
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food
UDS	Unscheduled DNA Synthesis
WHO	World Health Organisation