This substance is an aromatic compound with a sulfide group in an unsaturated side-chain; it was assigned to structural class III because it is not a common component of food.

Data for methyl sulfide (no. 452; subgroup i) were also considered relevant for assessing the toxicity of compounds with simple side-chains (e.g. nos 461–463, 465–469, 472–481, 495–497 and 500–503).

Although 2-(methylthiomethyl)-3-phenylpropenal (no. 505) is not an aryl thioether, the safety margin between its NOEL and the intake of *o*-(methylthio)phenol (no. 503) was considered to be adequate. The NOEL for 2-(methylthiomethyl)-3-phenylpropenal (no. 505) did not provide an adequate margin of safety for methyl 3-(methylthio)propionate (no. 472) at the current estimated level of intake, but the simple side-chain acid and ester were predicted to be of low toxicity and the NOEL for methyl sulfide (no. 452; subgroup i) was considered to provide an adequate safety margin. The NOELs for 2-(methylthiomethyl)-3-phenylpropenal (no. 505) and methyl sulfide (no. 452; subgroup i) were considered inappropriate for evaluating the toxicity of two α, β-unsaturated carbonyls (nos 470 and 471) because the latter substances are potentially more reactive and toxic. The evaluation of the two α, β-unsaturated carbonyls (nos 470 and 471) therefore proceeded to step B5.

Subgroup iii — cyclic sulfides. This subgroup comprises eight cyclic thioethers. NOELs of 0.44 mg/kg of body weight per day for 2-methyl-4-propyl-1,3-oxathiane (no. 464), 9.2 mg/kg of body weight per day for 4,5-dihydro-3(2*H*)-thiophenone (dihydro-3(2*H*)-thiophenone; no. 498), 7 mg/kg of body weight per day for 2-methyl-1,3-dithiolane (no. 534), 0.21 mg/kg of body weight per day for 2,2,4,4,6,6-hexamethyl-1,3,5-trithiane (no. 543) and 3.1 mg/kg of body weight per day for 2,5-dimethyl-2,5-dihydroxy-1,4-dithiane (2,5-dimethyl-1,4-dithiane-2,5-diol; no. 562) were reported. These values were considered to provide an adequate margin of safety for evaluating the toxicity of substance nos 456, 499 and 550.

Subgroup iv — simple thiols. This subgroup comprises 24 simple thiols. NOELs of 0.56 mg/kg of body weight per day for cyclopentanethiol (no. 516), 0.06 mg/kg of body weight per day for a mixture of 2-, 3- and 10-mercaptopinane (mixture of 2,6,6-trimethylbicyclo(3.1.1)heptane-2-, 3- and 10-thiols; no. 520), 0.52 mg/kg of body weight per day for *o*-toluenethiol (no. 528), 0.43 mg/kg of body weight per day for 2,6-dimethylthiophenol (2,6-dimethylbenzenethiol; no. 530) and 3.4 mg/kg of body weight per day for 2-naphthalenethiol (no. 531) were reported. These values were considered to provide an adequate margin of safety for the individual substances and for the other structurally related thiols in subgroup iv (nos 508–515, 517–519,

521–527, 529) in relation to current estimates of intake, with the exception of the mixture of 2-, 3- and 10-mercaptopinane (no. 520). A margin of safety of about 300 (based on an estimated per capita intake of 0.2μg/kg of body weight per day in the USA) was obtained from the results of a 90-day study in which a single dose of 0.06mg/kg of body weight per day was tested. This substance was therefore also evaluated by comparison with other substances in this subgroup (nos 516, 528, 530 and 531), for which there was an adequate margin of safety. The Committee noted that nos 521–524 are unsaturated thiols. Of these, allyl mercaptan (no. 521) would be predicted to be more toxic than thiols that have double bonds in different positions (by analogy with their oxygenated analogues). Although no data were available on the toxicity of allyl mercaptan (no. 521), the NOEL for diallyl trisulfide (no. 587; subgroup ix), which would be converted to allyl mercaptan after reduction to allyl disulfide, was 4.6mg/kg of body weight per day in a 90-day study in rats. This NOEL was considered to provide an adequate margin of safety for substance nos 521–524.

Subgroup v — thiols with oxidized side-chains. This subgroup comprises 18 thiols with oxygenated side-chains. NOELs of 1.9mg/kg of body weight per day for 2-mercapto-3-butanol ((*R*,*S*)-3-mercaptobutan-2-ol; no. 546) and 3-mercapto-2-pentanone (no. 560), and 2.8mg/kg of body weight per day for α-methyl-β-hydroxypropyl α-methyl-β-mercaptopropyl sulfide (3-[(2-mercapto-1-methylpropyl)thio]-2-butanol; no. 547) were reported. These levels were considered to provide an adequate margin of safety for the other flavouring agents in this subgroup (nos 544, 545, 548, 549, 551–559, 561, 563), including the one substance in structural class III, sodium 3-mercapto-oxopropionate (no. 563). Although the latter compound has more than three functional groups, the oxopropionate moiety would have little toxic potential, and the NOELs for substance nos 546, 547 and 560 were considered to provide an adequate margin of safety.

Subgroup vi — dithiols. This subgroup comprises nine dithiols. The NOEL for both 2,3-butanedithiol (no. 539) and 1,8-octanedithiol (octane-1,8-dithiol; no. 541) was 0.7mg/kg of body weight per day, which was considered to provide an adequate margin of safety for the other substances in the subgroup (nos 532, 535–538, 540, 542).

Subgroup vii — simple disulfides. This subgroup comprises 14 disulfides. The major metabolites of the unsaturated disulfides in this subgroup would be thiols. The NOELs were 7.3mg/kg of body weight per day for propyl disulfide (no. 566), 0.23mg/kg of body weight per day for dicyclohexyl disulfide (no. 575) and 1.2mg/kg of body weight per day for benzyl methyl disulfide (no. 577). These values provide an adequate margin of safety for these substances as well as for seven

structurally related substances (nos 564, 565, 567, 569–571 and 579) at currently estimated levels of intake. NOELs were not available for the unsaturated or aryl disulfides in this subgroup, but the aryl disulfides, methyl phenyl disulfide (no. 576) and phenyl disulfide (no. 578), would be rapidly reduced to thiophenol, and the NOEL of 3.4 mg/kg of body weight per day for 2-naphthalenethiol (no. 531; subgroup iv) was considered to provide an adequate margin of safety for these agents.

The Committee was aware that propenyl disulfides can cause haemolytic anaemia in certain species after short-term exposure. This effect would be of concern to susceptible individuals. Substance nos 568 and 572 would be metabolized to allyl mercaptan (no. 521; subgroup iv). The Committee noted that the NOEL for diallyl trisulfide (no. 587; subgroup ix) in a 90-day study in rats given a single dose was 4.6 mg/kg of body weight per day, and considered that this would provide an adequate margin of safety for the allyl thiol produced on reduction of substance nos 568 and 572. A closely related substance, di(1-propenyl) disulfide, was about four times as potent as allyl disulfide (no. 572) and about 20 times as potent as propyl disulfide (no. 566). The intakes of the related propenyl and butenyl disulfides (nos 569–571) gave safety margins of greater than 50000 in comparison with the NOEL for propyl disulfide (no. 566), and this was considered to be adequate to allow for the differences in potency.

Subgroup viii — disulfides with oxidized side-chains. This subgroup consists of two disulfides with oxidized side-chains, 2-methyl-2-(methyldithio)propanal (no. 580) and ethyl 2-(methyldithio)propionate (no. 581). Since the toxicity of these agents has not been studied, the Committee compared these substances with the simple disulfides (subgroup vii) and concluded that adequate margins of safety were available, given their greater polarity and the presence of thiols with and without oxidized side-chains, i.e. subgroups iv and v.

Subgroup ix — trisulfides and polysulfides. This subgroup consists of six trisulfides and one polysulfide. NOELs of 4.8 mg/kg of body weight per day for dipropyl trisulfide (no. 585) and 4.6 mg/kg of body weight per day for diallyl trisulfide (no. 587) were reported, which gave an adequate margin of safety for these and the other substances in this subgroup (nos 582–584, 586 and 588).

Subgroup x — heterocyclic disulfides. This subgroup comprises two heterocyclic disulfides. The NOEL of 1.9 mg/kg of body weight per day for 3,5-dimethyl-1,2,4-trithiolane (no. 573) provides an adequate margin of safety for this substance at current levels of use. 3-Methyl-1,2,4-trithiane (no. 574) was reported to have no effect at the single dose of 0.3 mg/kg of body weight per day in a 90-day study. This dose provides

a margin of safety of only 100 in relation to the estimated per capita intake level of 1 μg/kg of body weight per day in the USA, but the NOEL for the closely related compound 3,5-dimethyl-1,2,4-trithiolane (no. 573) provides a margin of safety greater than 1000.

Subgroup xi — thioesters. This subgroup consists of 15 thioesters. The NOELs of 6.5 mg/kg of body weight per day for ethyl thioacetate (*S*-ethyl ethanethioate; no. 483) and 1000 mg/kg of body weight per day for methyl thiobutyrate (*S*-methyl butanethioate; no. 484) were considered to provide an adequate margin of safety for all other esters in this group. The Committee concluded that the current intake levels of allyl thiopropionate (*S*-2-propenyl propanethioate; no. 490) and prenyl thioacetate (no. 491) are safe on the basis of the NOEL of 4.6 mg/kg of body weight per day for diallyl trisulfide (no. 587; subgroup ix), which is predicted to be metabolized initially to allyl disulfide and then to allyl mercaptan.

Subgroup xii — sulfoxides. This subgroup consists of only one sulfoxide, methylsulfinylmethane (no. 507). The NOEL in monkeys given methylsulfinylmethane by gavage for 74–87 weeks was 3000 mg/kg of body weight per day. The Committee concluded that this NOEL and other data from studies in rats, dogs and humans provide an adequate margin of safety for the use of methylsulfinylmethane as a flavouring agent at the estimated daily per capita intake of 0.00001 μg/kg of body weight per day in the USA.

Step B5

Five substances, allyl sulfide (no. 458), methyl phenyl sulfide (no. 459), benzyl methyl sulfide (no. 460), 2-[(methylthio)methyl]-2-butenal (no. 470) and 2,8-dithianon-4-ene-4-carboxaldehyde (5-methylthio-2[(methylthio)methyl]-2-pentenal; no. 471), were evaluated at this step of the Procedure. The daily per capita intake of all five substances is less than 1.5 μg per day in both Europe and the USA. The Committee applied the criteria for step B5 outlined in Annex 5 of the safety evaluation of its forty-ninth meeting (Annex 1, reference *132*) and concluded that use of these substances at their current levels of intake raises no concern about safety.

Summary

In summary, for 100 agents in subgroups iii–xii, a NOEL was available for the substance, a closely related substance or a predicted major metabolite which provided an adequate margin of safety (>1000). For six of nine agents in subgroup i and 26 of 28 agents in subgroup ii, a NOEL was available for the substance or a closely related substance that provided a margin of safety >1000. Therefore, the Committee determined at step B4 of the Procedure that the safety of these 132

substances would not be expected to be a concern when they were used at their current estimated levels of daily intake. The evaluation of the remaining five substances (nos 458–460 in subgroup i and nos 470 and 471 in subgroup ii) proceeded to step B5 of the Procedure. The Committee concluded that use of these substances at their current levels of intake raises no concern about safety. The comparisons of toxicity and the data on intake for each subgroup which were used to apply steps B4 and B5 of the Procedure to the evaluation of individual substances in this group of flavouring agents are summarized in Tables 1 and 2.

4.1.4 *Consideration of combined intakes*

In the unlikely event that foods containing all 97 aliphatic and aromatic sulfides and thiols in structural class I were to be consumed simultaneously on a daily basis, the estimated total daily per capita intake would not exceed the threshold for human intake for substances in class I (1800μg). In the unlikely event that foods containing all 34 aliphatic and aromatic sulfides in structural class II and all six aliphatic and aromatic sulfides in structural class III were to be consumed simultaneously on a daily basis, the estimated total daily per capita intake would not exceed the threshold for human intake for flavouring agents in classes II and III (540μg and 90μg, respectively). The Committee noted that the powerful aroma of these substances limits the level of their use in foods.

4.1.5 *Conclusions*

The Committee concluded that the 137 flavouring agents comprising aliphatic and aromatic sulfides and thiols evaluated at the present meeting could not be predicted to be metabolized to innocuous products. According to the Procedure, data on toxicity were needed to evaluate the safety of this group of flavouring agents. The primary data that were used in the evaluations consisted of 27 short-term studies (lasting at least 90 days) in rats or monkeys for 25 of the substances and a short-term study in dogs and a long-term study in rats for one substance (no. 507, methylsulfinylmethane). Most of these studies were conducted using single or multiple doses which had no effects. The NOELs were therefore derived from studies in which no toxic effects were seen.

On the basis of the available toxicity data on representative substances in each subgroup and on their metabolism, the Committee concluded that 132 of the flavouring agents are of no safety concern when used at their current levels of estimated intake. The remaining five substances were considered to be of no safety concern at intake levels of < 1.5μg per day.

Other toxicity data, including the results of short-term toxicity tests and developmental toxicity and genotoxicity studies, were consistent with the results of the evaluation conducted using the Procedure. A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.2 Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups

The Committee evaluated a group of 47 flavouring agents that included aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (Table 3) using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1).

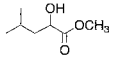
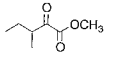
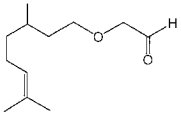
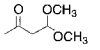
Eight of these substances (nos 589, 591, 603 and 631–635) are α-keto acids, esters or related substances; five (nos 590 and 619–622) are α-hydroxy acids, esters or related substances; 14 (nos 592–602, 604, 614 and 615) are β-keto or β-hydroxy alcohols, aldehydes, carboxylic acids or their related acetals or esters; five (nos 605–609) are γ-keto acids, esters or related substances; four (nos 610–613) are ω-substituted alcohols, aldehydes or acetals; and 18 (nos 614–631) are simple, aliphatic di- or tricarboxylic acids or their esters.

The Committee had evaluated three members of this group previously for other functional uses. Fumaric acid ((2*E*)-2-butenedioic acid; no. 618) was first considered by the Committee at its tenth meeting (Annex 1, reference *13*); at its thirty-fifth meeting (Annex 1, reference *88*), the Committee established a group ADI "not specified"[1] for fumaric acid and its salts. Triethyl citrate (triethyl 2-hydroxy-1,2,3-propanetricarboxylate; no. 629) was first considered by the Committee at its twenty-third meeting (Annex 1, reference *50*); at its twenty-eighth meeting (Annex 1, reference *66*), the Committee established an ADI of 0–20 mg/kg of body weight. Diethyl tartrate (diethyl 2,3-dihydroxybutanedioate; no. 622) was first considered by the Committee at its twenty-third meeting (Annex 1, reference *50*), when it determined that an evaluation was not possible on the basis of the data available at that time. As no additional data were available to the Committee at its twenty-fifth meeting (Annex 1, reference *56*), no ADI was allocated. The Committee also evaluated terpenoid flavouring agents related to this group, including linalool, linalyl acetate, citronellol, citral and geranyl acetate, at its twenty-third meeting and established a group ADI of 0–0.5 mg/kg of body weight, expressed as citral (Annex 1, reference *50*).

[1] See page 22.

Table 3

Summary of the results of the safety evaluation of 47 aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups[a]

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
2-Oxobutyric acid (2-oxobutanoic acid)	589	600-18-0 	No Europe: 0.03 USA: 2	NR	NR	No safety concern
Methyl 2-hydroxy-4-methyl-pentanoate (methyl 2-hydroxy-4-methylvalerate)	590	40348-72-9 	No Europe: ND USA: 0.8	NR	NR	
Methyl 2-oxo-3-methyl-pentanoate (methyl 3-methyl-2-oxo-pentanoate)	591	3682-42-6 	No Europe: ND USA: 19	NR	NR	
Citronelloxyacetaldehyde ([(3,7-dimethyl-6-octenyl) oxy]-acetaldehyde)	592	7492-67-3 	No Europe: 34 USA: 0.1	NR	NR	
3-Oxobutanal dimethyl acetal (4,4-dimethoxy-2-butanone)	593	5436-21-5 	No Europe: 0.01 USA: 0.1	NR	NR	
Ethyl 3-hydroxybutyrate	594	5405-41-4 	No Europe: 12 USA: 29	NR	NR	

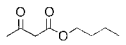
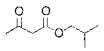
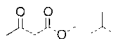
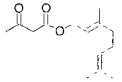
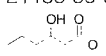
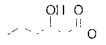
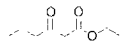
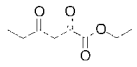
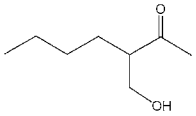
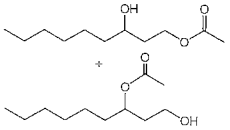
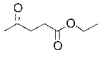
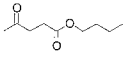
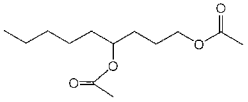
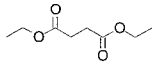
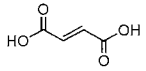
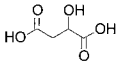
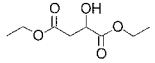
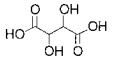
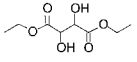
Ethyl acetoacetate	595	141-97-9 	Yes Europe: 1900 USA: 3900	Yes[d]	NR	No safety concern
Butyl acetoacetate	596	591-60-6 	No Europe: 98 USA: 6	NR	NR	
Isobutyl acetoacetate	597	7779-75-1 	No Europe: ND USA: 4	NR	NR	
Isoamyl acetoacetate (isopentyl acetoacetate)	598	2308-18-1 	No Europe: ND USA: 11	NR	NR	
Geranyl acetoacetate (3,7-dimethyl-2,6-octadienyl acetoacetate)	599	10032-00-5 	No Europe: ND USA: 0.04	NR	NR	
Methyl 3-hydroxyhexanoate	600	21188-58-9 	No Europe: 1 USA: 1	NR	NR	
Ethyl 3-hydroxyhexanoate	601	2305-25-1 	No Europe: 93 USA: 0.1	NR	NR	
Ethyl 3-oxohexanoate	602	3249-68-1 	No Europe: 0.04 USA: 1	NR	NR	
Ethyl 2,4-dioxohexanoate	603	13246-52-1 	No Europe: ND USA: 0.02	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
3-(Hydroxymethyl)-2-heptanone	604	65405-68-7 	No Europe: 38 USA: 8	NR	NR	No safety concern
1,3-Nonanediol acetate (mixed esters) (1,3-nonanediol monoacetate)	605	1322-17-4 	No Europe: 15 USA: 8	NR	NR	
Levulinic acid (4-oxopentanoic acid)	606	123-76-2 	No Europe: 1600 USA: 1200	NR	NR	
Ethyl levulinate (ethyl 4-oxopentanoate)	607	539-88-8 	No Europe: 740 USA: 84	NR	NR	
Butyl levulinate (butyl 4-oxopentanoate)	608	2052-15-5 	No Europe: ND USA: 3	NR	NR	
1,4-Nonanediol diacetate	609	67715-81-5 	No Europe: 0.06 USA: 0.4	NR	NR	

Hydroxycitronellol (3,7-dimethyloctane-1,7-diol)	610	107-74-4 	No Europe: 11 USA: 6	NR	NR	No safety concern
Hydroxycitronellal (7-hydroxy-3,7-dimethyloctanal)	611	107-75-5 	No Europe: 28 USA: 30	NR	NR	
Hydroxycitronellal dimethyl acetal (8,8-dimethoxy-2,6-dimethyl-2-octanol)	612	141-92-4 	No Europe: 0.04 USA: 0.8	NR	NR	
Hydroxycitronellal diethyl acetal (8,8-diethoxy-2,6-dimethyloctan-2-ol)	613	7779-94-4 	No Europe: 0.01 USA: 2	NR	NR	
Diethyl malonate (diethyl propanedioate)	614	105-53-3 	No Europe: 760 USA: 370	NR	NR	
Butyl ethyl malonate (butyl ethyl propanedioate)	615	17373-84-1 	No Europe: ND USA: 0.1	NR	NR	
Dimethyl succinate (dimethyl butanedioate)	616	106-65-0 	No Europe: 78 USA: 120	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
Diethyl succinate (diethyl butanedioate)	617	123-25-1 	No Europe: 150 USA: 180	NR	NR	No safety concern
Fumaric acid[e] ((2*E*)-2-butenedioic acid)	618	110-17-8 	Yes Europe: 920 USA: 220000	Yes[f]	NR	
(–)-Malic acid ((2*S*)-hydroxybutanedioic acid)	619	97-67-6 	Yes Europe: 16000 USA: 58000	Yes[e]	NR	
Diethyl malate (diethyl hydroxybutanedioate)	620	7554-12-3 	No Europe: 5 USA: 34	NR	NR	
Mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (mixture of (+)-, (–)-, (+/–)- and meso-2,3-dihydroxybutanedioic acid)	621	87-69-4 	Yes Europe: 4400 USA: 14000	No	Yes; the NOEL of 1200 mg/kg of body weight per day reported in a 2-year study in rats is >1000 times the daily per capita intake	
Diethyl tartrate (diethyl 2,3-dihydroxybutanedioate)	622	87-91-2 	No Europe: 17 USA: 0.02	NR	NR	

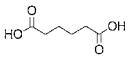
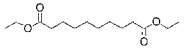
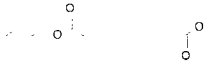
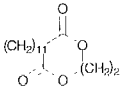
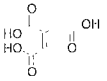
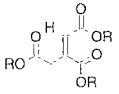
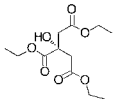
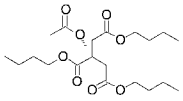
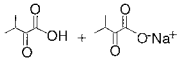
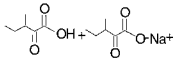
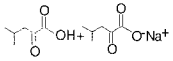
Adipic acid (hexanedioic acid)	623	124-04-9 	Yes Europe: 12 USA: 18000	No	Yes; the NOEL of 6200 mg/kg of body weight per day reported for the structurally related substance, dibutyl sebacate, in a 2-year study in rats is >10000 times the daily per capita intake	No safety concern
Diethyl sebacate (diethyl decanedioate)	624	110-40-7 	No Europe: 135 USA: 76	NR	NR	
Dibutyl sebacate (dibutyl decanedioate)	625	109-43-3 	No Europe: ND USA: 0.08	NR	NR	
Ethylene brassylate (1,4-dioxacycloheptadecane-5,17-dione)	626	105-95-3 	No Europe: 4 USA: 0.8	NR	NR	
Aconitic acid (1-propene-1,2,3-tricarboxylic acid)	627	499-12-7 	No Europe: 0.01 USA: 0.02	NR	NR	
Ethyl aconitate (mixed esters) (ethyl 1-propene-1,2,3-tricarboxylate)	628	1321-30-8  R = C_2H_5	No Europe: ND USA: 4	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
Triethyl citrate[e] (triethyl 2-hydroxy-1,2,3-propanetricarboxylate)	629	77-93-0 	Yes Europe: 3400 USA: 2400	Yes[f]	NR	No safety concern
Tributyl acetylcitrate (tributyl 2-(acetyloxy)-1,2,3-propanetricarboxylate)	630	77-90-7 	No Europe: ND USA: 0.4	NR	NR	
3-Methyl-2-oxobutanoic acid and its sodium salt	631	759-05-7 and 3715-29-5 	No Europe: 0.01 USA: 0.2	NR	NR	
3-Methyl-2-oxopentanoic acid and its sodium salt	632	1460-34-0 and 66872-74-0 	No Europe: ND USA: 0.2	NR	NR	

4-Methyl-2-oxopentanoic acid and its sodium salt	633	816-66-0 and 4502-00-5 	No Europe: ND USA: 0.2	NR	NR	No safety concern
2-Oxopentanedioic acid	634	328-50-7 	No Europe: ND USA: 0.2	NR	NR	
3-Hydroxy-2-oxopropionic acid	635	1113-60-6 	No Europe: ND USA: 0.2	NR	NR	

CAS: Chemical Abstracts Service; ND: no data available; NR: not required for evaluation because an adequate NOEL for the substance or a related substance was identified at step A3 or A4 of the Procedure.

[a] *Step 1*: All of the substances in this group are in structural class I.
Step 2: All of the substances in this group are metabolized to innocuous products.

[b] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 7, 1999). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The threshold for human intake of class I is 1800 μg per day. All intake values are expressed in μg per day.

[d] Ethyl acetoacetate is expected to be hydrolysed to acetoacetic acid, which is endogenous in humans.

[e] The ADI for this substance was maintained.

[f] Fumaric acid, (–)-malic acid and triethyl citrate are components of the tricarboxylic acid cycle.