European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 35, Revision 1 (FGE.35Rev1): Three quinine salts from the Priority list from chemical group 30[1]

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

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ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to evaluate three flavouring substances in the Flavouring Group Evaluation 35, Revision 1, using the Procedure in Commission Regulation (EC) No 1565/2000. The present revision includes new specification data on quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155], new intake data on all three candidate substances and toxicological and genotoxicity data on quinine hydrochloride [FL-no: 14.011] and quinine monohydrochloride dihydrate [FL-no: 14.155], as well as two structurally related quinine salts (quinine dihydrochloride and deoxyquinine). A search in open literature has been made and the relevant data are presented. This evaluation concerns only the use of these quinine salts in beverages, where they are legally permitted. Because of the availability of well conducted human studies at much higher quinine exposures than those occurring when quinine is used as flavouring substance and which were considered in this FGE.35Rev1, the Panel considered the use of the Procedure for these substances inappropriate. However, based on human data available on quinine, the Panel concluded that the quinine salts are not expected to be of safety concern at their estimated level of intake as flavouring substances, provided that hypersensitivity reactions are avoided by the legally required labelling of quinine-containing beverages. The Panel noted that a very high intake (e.g. more than 1 litre) of non-alcoholic beverages containing quinine or its salts at the maximum permitted level could result in adverse health effects in humans. Besides the safety assessment of these three flavouring substances, the specifications for the materials of commerce have also been considered. Adequate specifications, including complete purity criteria and identity, have been provided for all three candidate substances.

KEY WORDS

flavourings, food safety, quinine salts, FGE.35

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[1] On request from the European Commission, Question No EFSA-Q-2011-01033, EFSA-Q-2011-01034 and EFSA-Q-2011-01035, adopted on 09 September 2015.

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SUMMARY

Following a request from the European Commission, the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) was asked to deliver a scientific opinion on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to evaluate three flavouring substances in the Flavouring Group Evaluation 35, Revision 1 (FGE.35Rev1), using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These three flavouring substances belong to chemical group 30 of Annex I of the Commission Regulation (EC) No 1565/2000.

Compared with FGE.35 consisting of three candidate substances, all being salts of quinine from the priority list, FGE.35 Revision 1 includes specification data on quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155], new intake data on all three candidate substances and toxicological and genotoxicity data on quinine hydrochloride [FL-no: 14.011] and two structurally related quinine salts.

The quinine component is the (−)-isomer, which has (8S,9R)-configuration.

All three substances are classified into structural class III and do not naturally occur in food.

Because the three candidate substances are water-soluble salts of the same flavouring component, quinine, and because they are expected to replace each other, the Panel decided to carry out the safety assessment on the basis of exposure to quinine equivalents.

In its evaluation, the Panel, as a default, used the "Maximised Survey-derived Daily Intake" (MSDI) approach to estimate the per capita intakes of the flavouring substances in Europe. However, when the Panel examined the information provided by the European 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.

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

On the basis of the genotoxicity data available on the quinine salts the Panel concluded that there is no concern for genotoxicity for the candidate substances, when used as flavouring substances.

The Panel considered a well conducted 21-day study in humans, with much higher levels of exposure to quinine than those resulting from its use as flavouring substance at levels reported in this FGE.35Rev1 (i.e. MSDI of 745 µg per capita per day (expressed as quinine equivalents) or a highest mTAMDI of 29100 µg quinine equivalents per person per day for [FL-no: 14.011]), providing a no observed adverse effect level (NOAEL) of 72 mg quinine equivalents/person/day. Because of the availability of this study and the knowledge of quinine toxicity following its use as an anti-malarial agent, the Panel decided that the Procedure for the evaluation of flavouring substances, as laid down in Commission Regulation (EC) No 1565/2000, is not applicable. The Panel considered the use of quinine at levels of exposures as indicated by the mTAMDI not of safety concern. The mTAMDI is

expected to reliably reflect the use of quinine because its consumption is limited to only two food categories: alcoholic and non-alcoholic beverages.

These exposure levels are equivalent to a daily consumption of approximately 300 ml of non-alcoholic beverages containing quinine at the maximum permitted level of 100 mg/l. The margin of safety is approximately 100 for the MSDI and 2.5 for the mTAMDI.

The Panel noted that a very high intake (e.g. more than 1 litre) of non-alcoholic beverages containing quinine or its salts at the maximum permitted level could result in adverse health effects in human.

In order to determine whether the conclusion for the candidate substances can be applied to the material of commerce, it is necessary to consider the available specifications. Specifications, including purity criteria and identity for the materials of commerce, have been provided for all three candidate substances.

Accordingly, the three flavouring substances, quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155], would present no safety concern at the levels of intake estimated on the basis of the MSDI or mTAMDI approach. The Panel addressed in this evaluation only those food categories (14.1 and 14.2) in which the use of quinine is permitted according to Annex I of regulation 1334/2008. Therefore, this evaluation is applicable for the use of quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155] in alcoholic and non-alcoholic beverages.

Considering the occurrence of hypersensitivity against quinine in the human population, the Panel would support continuation of the legal requirement for labelling of quinine-flavoured foods

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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 evaluated three quinine salts in the Flavouring Group Evaluation 35 (FGE.35). The Opinion was adopted on 22 may 2008. EFSA concluded that the final evaluation could not be performed for the substance quinine hydrochloride [FL-no: 14.011], as data for production volumes as flavouring substance in order to calculate an MSDI were missing. Furthermore, for quinine hydrochloride [FL-no: 14.011] and quinine sulphate [FL-no: 14.152] use levels were required in order to calculate the mTAMDIs in order to conclude whether more refined exposure assessments are needed and to finalise the evaluation. For quinine monohydrochloride dihydrate [FL-no: 14.155] more reliable exposure data were required in order to finalise the evaluation.

The requested information has now been submitted by the applicant.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requests European Food Safety Authority (EFSA) to evaluate the new information and, depending on the outcome, proceed to the full evaluation on this flavouring substance in accordance with Commission Regulation (EC) No 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

1. History of the evaluation of the substances in the present Flavouring Group Evaluation

The first version of the Flavouring Group Evaluation (FGE) 35 (FGE.35) dealt with three quinine salts. For quinine hydrochloride [FL-no: 14.011] the evaluation could not be finalised, as data for production volumes as flavouring substance, in order to calculate an Maximised Survey-derived Daily Intake (MSDI), were missing. Furthermore, the specifications were not adequate for quinine sulphate [FL-no: 14.152] (minimum assay is missing) or for quinine monohydrochloride dihydrate [FL-no: 14.155] (the composition of the secondary components to be specified).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.35	22 May 2008	http://www.efsa.europa.eu/en/efsajournal/pub/739.htm	3
FGE.35Rev1			3

The present revision of FGE.35 (FGE.35Rev1) is a complete revision of the first version and includes assessment of new updated use levels for three substances [FL-no: 14.011, 14.152 and 14.155] and new tonnage figure for one substance [FL-no: 14.155] provided by Industry (UNESDA, 2011). Specifications have also been provided by Industry (EFFA, 2012). Industry has also provided new genotoxicity studies with quinine. This information has been included in this evaluation. A search in open literature has been made and the relevant data are presented here.

2. Presentation of the substances in Flavouring Group Evaluation 35, Revision 1

2.1. Description

The present revision of FGE.35Rev1 deals with three salts of quinine, quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155] from European Union (EU) chemical group 30, Annex I of Commission Regulation (EC) No 1565/2000. The three flavouring candidate substances under consideration, as well as their chemical register names, Flavour Information System (FLAVIS (FL)), Chemical Abstracts Service (CAS), Council of Europe (CoE) and Flavor and Extract Manufacturers Association (FEMA) numbers, structure and specifications, are listed in Table 1. Quinine is permitted to be used in only alcoholic and non-alcoholic beverages, at maximum use levels of 250 and 100 mg/kg, respectively.[7] In addition, quinine-containing beverages need to be labelled as such.[8]

Because the three candidate substances are water-soluble salts of the same flavouring component, quinine, and because they are expected to replace each other in beverages, the Panel decided to treat them as one substance in this opinion.

2.2. Previous evaluation by other authority within the European Union

The Bundesinstitut für Risikobewertung (BfR) evaluated, in 2005, the safety of quinine in food, in particular the available data on possible effects during pregnancy (BfR, 2008). It concluded that there were several groups with enhanced risk, such as individuals with hypersensitivity to quinine,

[7] 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.

[8] Regulation (EC) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304, 22.11.2011, p. 18–63.

glucose-6-phosphate deficiency, myasthenia gravis or tinnitus/optic nerve damage, as well as pregnant women. Most undesired effects were observed at doses more than 10-fold above 100 mg/person/day, which was assumed by the BfR as a possible worst-case exposure scenario. BfR advises, for precautionary reasons, pregnant women to refrain from the use of quinine-containing foods; further, it proposed a public campaign to make consumers aware of the potential risks of the intake of (high amounts of) quinine-containing foods.

2.3. Stereoisomers

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

The configurations of the quinine component in this FGE is the (−)-isomer, which has (8*S*,9*R*)-configuration.

2.4. Natural occurrence in food

Quinine does not occur naturally in food (TNO, 2011).

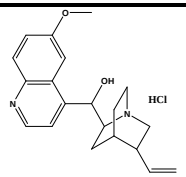
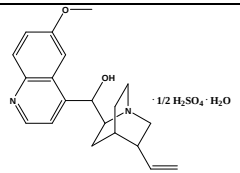
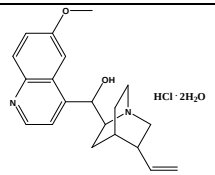
3. Specifications

Purity criteria for the three candidate substances have been provided by the Flavour Industry (Flavour Industry, 2011) (see Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000, the information is adequate for the three candidate substances (see Section 2.2 and Table 1).

SUMMARY OF SPECIFICATION DATA

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 35, Revision 1

FL-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]	Specification comments
14.011	Quinine hydrochloride		2976 715 130-89-2	Solid $C_{20}H_{24}N_2O_2$ HCl 360.92	Soluble Freely soluble	 115–116 NMR MS 95%	n.a. n.a.	
14.152	Quinine sulphate		2977 804-63-7	Solid $(C_{20}H_{24}N_2O_2)_2$ H_2SO_4 $2H_2O$ 782.96	Soluble Soluble	 225 IR 98%	n.a. n.a.	
14.155	Quinine monohydrochloride dihydrate		 6119-47-7	Solid $C_{20}H_{24}N_2O_2$ HCl $2H_2O$ 396.92	Soluble Very soluble	 115–116 NMR 99%	n.a. n.a.	

(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.

4. Intake data

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

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

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

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

One of the alternatives is the "Theoretical Added Maximum Daily Intake" (TAMDI) approach, which is calculated on the basis of standard portions and upper use levels (SCF, 1995) for flavourable beverages and foods in general, with exceptional levels for particular foods. This method is regarded as a conservative estimate of the actual intake by most consumers because it is based on the assumption that the consumer regularly eats and drinks several food products containing the same flavouring substance at the upper use level.

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

4.1. Estimated daily *per capita* intake (MSDI approach)

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

Average *per capita* intake (MSDI) is estimated on the assumption that the amount added to food is consumed by 10 % of the population[9] (Eurostat, 1998). This is derived for candidate substances from estimates of annual volume of production provided by Industry and incorporates a correction factor of 0.6 to allow for incomplete reporting (60 %) in the Industry surveys (SCF, 1999).

The total annual volume of production of the three candidate substances in the present Flavouring Group Evaluation (FGE.35Rev1) from use as flavouring substances in Europe has been reported to be approximately 6 900 kg (Flavour Industry, 2011). About 94 % of the total annual volume of production for the candidate substances is accounted for by quinine hydrochloride [FL-no: 14.011].

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

The intake of all three candidates has been expressed in equivalents of quinine. The conversion factors are 0.898 for quinine hydrochloride, 0.828 for the sulphate salt and 0.816 for the $HCl.2H_2O$ salt).

On the basis of the annual volume of production reported for the candidate substances, MSDI values for each of these flavourings have been estimated (Table 3). The estimated daily per capita intake of quinine hydrochloride [FL-no: 14.011] from use as a flavouring substance is 790 µg (= 709 µg quinine equivalents), while for quinine sulphate [FL-no: 14.152] it is 0.13 µg (= 0.11 µg quinine equivalents) and for quinine monohydrochloride dihydrate [FL-no: 14.155] it is 45 µg (= 36.7 µg quinine equivalents) (Table 4). This adds up to 746 µg quinine equivalents per capita per day.

4.2. Intake estimated on the basis of the modified TAMDI (mTAMDI)

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

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

For the present evaluation of the three candidate substances, information on food categories and normal and maximum use levels[10,11,12] were submitted by Industry (Flavour Industry, 2011). The three candidate substances are used in flavoured food products, which are divided into the food categories outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000a), as shown in Table 2. For the present calculation of mTAMDI, the reported normal use levels were used. In cases where different use levels were reported for different food categories the highest reported normal use level was used. Use levels were provided for the food categories 01.0, 03.0, 05.0, 07.0, 14.1 and 14.2 (see Table 2 and Appendix B Table B.1.2). However, since, according to Regulation (EC) No 1334/2008, the use of quinine is not allowed in food categories 01.0, 03.0, 05.0 and 07.0 (EC, 2008), contribution from these food categories is not included in the mTAMDI calculation (see Appendix B).

Table 2: Use of candidate substances

Food category	Description	Flavourings used*
01.0	Dairy products, excluding products of category 2	All
02.0	Fats and oils, and fat emulsions (type water-in-oil)	None
03.0	Edible ices, including sherbet and sorbet	All
04.1	Processed fruits	None
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	None
05.0	Confectionery	All
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	None
07.0	Bakery wares	All
08.0	Meat and meat products, including poultry and game	None
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	None
10.0	Eggs and egg products	None
11.0	Sweeteners, including honey	None
12.0	Salts, spices, soups, sauces, salads, protein products etc.	None
13.0	Foodstuffs intended for particular nutritional uses	None
14.1	Non-alcoholic (“soft”) beverages, excl. dairy products	All

[10] “Normal use” is defined as the average of reported usages and “maximum use” is defined as the 95th percentile of reported usages (EFFA, 2002).

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

[12] The use levels from food category 5 “Confectionery” have been inserted as default values for food category 14.2 “Alcoholic beverages” for substances for which no data have been given for food category 14.2 (EFFA, 2007).

Table 2: Use of candidate substances

Food category	Description	Flavourings used*
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	All
15.0	Ready-to-eat savouries	None
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	None

*The Panel noted that the use in food categories 01.0, 03.0, 05.0 and 07.0, as reported by the Industry, is prohibited in the EU.

The Panel noted that the use in food categories 01.0, 03.0, 05.0 and 07.0, as reported by the Industry, is prohibited in the EU.

According to the Flavour Industry, the normal use levels and the maximum use levels for the candidate substances are in the same range of 10–100 mg/kg (Flavour Industry, 2011).

The mTAMDI value is 32 400 µg named substance/person/day for each of the three candidate substance from structural class III based on the use in food categories 14.1 and 14.2 (see also Table 4). The mTAMDI is expected to reliably reflect the exposure to quinine because its consumption is limited to only two food categories: alcoholic and non-alcoholic beverages.

For detailed information on use levels and intake estimations based on the mTAMDI approach, see Section 7 and Appendix B.

5. Absorption, distribution, metabolism and elimination

Data on absorption, distribution and elimination of quinine in humans are available from the open literature. These data indicate that the substances in this group are well absorbed, mainly from the intestinal lumen, and are rapidly excreted. Major metabolites have been identified. However, the information on the metabolism of the substances in this flavouring group does not allow the conclusion that these substances will be metabolised to innocuous products.

For more detailed information, see Appendix C.

6. Safety evaluation of the flavouring substances

The Panel considered the use of the Procedure for these substances inappropriate for the following reasons:

- A well conducted 21-day study in humans was available, which used much higher quinine exposures than those resulting from the use as flavouring substance considered in this FGE.35Rev1.
- Data on the toxicity of quinine from its use as a therapeutic agent in malaria patients were available.

The Panel decided to use the above mentioned information for the safety assessment of quinine salts when used as flavouring substances.

7. Intake estimations based on the MSDI approach and the mTAMDI approach

The estimated intake of the three candidate substances [FL-nos: 14.011, 14.152 and 14.155], based on the mTAMDI, is 32 400 µg per person per day each named substance. For the individual substances the mTAMDIs are equivalent to 26 400–29 100 µg quinine equivalents/per person per day. The estimated intake of the three candidate substances [FL-nos: 14.011, 14.152 and 14.155], based on the MSDI, range from 0.13 to 790 µg per capita per day each named substance. For the individual substances the MSDIs are equivalent to 0.11–709 µg quinine equivalents/person/day (see Table 3).

Table 3: Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI (µg/*capita*/day)		mTAMDI (µg/person/day)	
		Named substance	quinine equivalents	Named substance	quinine equivalents
14.011	Quinine hydrochloride	790	709	32400	29100
14.152	Quinine sulphate	0.13	0.11	32400	26800
14.155	Quinine monohydrochloride dihydrate	45	36.7	32400	26400
-	Total quinine equivalents	-	746[(a)]		26400 - 29100[(b)]

(a): Based on summed production volume of quinine equivalents

(b): Based on use levels for the individual substances; hence, no summation of the mTAMDi of the individual substances

8. Considerations of combined intakes from use as flavouring substances

On the basis of the reported annual production volumes in Europe (Flavour Industry, 2011), the combined estimated daily *per capita* intake as flavourings of the three candidate substances [FL-nos: 14.011, 14.152 and 14.155] belonging to structural class III is 746 µg, expressed as total quinine equivalents. The mTAMDI values for each of the substances is 32 400 µg per person per day, which corresponds to exposures ranging from 26 400 to 29 100 µg quinine equivalents per person per day. These three flavouring substances can be used interchangeably, and the maximum amount of quinine equivalents will not be higher than indicated by the maximum use levels permitted. Therefore, the mTAMDIs cover, implicitly, the combined exposure to quinine from these three flavouring substances.

8.1. Acute toxicity

A dose of 2–8 g may be lethal in adults: fatalities have been reported after ingestion of these amounts; in children lower doses may be lethal (FDA, 2011).

8.2. Repeated dose toxicity studies

Since the three candidate quinine salts are water soluble, leading to freely dissolved quinine after ingestion, the toxicity data for each are valid for the other two. In the information that follows, the name “quinine” will be used to designate all three candidates.

The SCF assessed quinine in bitter drinks in 1988. Based on an estimated actual intake, on average, of 0.26 mg/person/day and assuming that for regular consumers of bitter drinks the mean daily intake unlikely will exceed 5 mg/person/day, the Committee concluded that up to a maximum of 100 mg/l of quinine in bitter drinks there were no objections (see Appendix D). This conclusion was based on a 90-day study in rats (report is no longer available to the Panel) as well as limited data on safety in volunteers (Zajtchuk et al., 1984; Worden et al., 1987), see below.

An important study to assess the safety of quinine was published by Drewitt et al. (1993). This study was not available to the SCF assessment of 1988. In this study, 32 healthy volunteers (20 males and 12 females, aged between 18 and 50 years) consumed either. lactose placebo or 80, 120 or 160 mg quinine hydrochloride daily for 21 days. The study was in full compliance with Good Clinical Practice and Good Laboratory Practice (GLP), and had a double-blind, four-way crossover design (i.e. every volunteer consumed each dose during 21 days, so that he/she was exposed a total of 63 days to quinine; however, each 21-day study was separated by at least two weeks to prevent carry-over). Every six hours volunteers consumed one-quarter of their daily quinine hydrochloride or lactose dose. During the study period, total urine was collected on days 0 (prior to study) 3, 7, 10, 14, 17 and 21. Blood samples were taken on the same days. Electrocardiograms (ECGs) and blood pressure were recorded, and extensive ophthalmic as well as audiometric measurements were carried out. The results showed that under these conditions the volume of urine was unaffected, the mean heart rate and blood pressure were within normal physiological limits and not significantly different from control values. The ECGs did not show abnormality. Furthermore, serum chemistry, haematology and urinalysis were within normal limits. Only some (reversible) changes were observed in ophthalmic parameters as measured by a very sensitive technique; thus, the incidence of transitory oculomotor oscillations (or

latent nystagmus) was increased when 120 and 160 mg of quinine hydrochloride were consumed. However, visual acuity was unaffected. No changes in auditory parameters were observed. The conclusion was that up to 80 mg quinine hydrochloride per day (divided over four administrations per day) was without adverse physiological, ophthalmic or audiometric effects. However, a daily intake of 120 mg quinine hydrochloride or more, resulting in serum quinine levels exceeding 0.65 µg/ml, increased background levels of oculomotor oscillations, and the incidence of ocular flutter was decreased. The no observed adverse effect level (NOAEL) for quinine hydrochloride was 80 mg/person/day, based on these ophthalmic findings. This NOAEL is equal to 72 mg quinine equivalents/person/day (Drewitt et al., 1993).

These results confirmed the conclusions from an earlier, more limited study (Worden et al., 1987) in which six male and 14 female volunteers (aged 18–53) received 100 or 120 mg quinine hydrochloride (provided in 1 000–1 250 ml tonic water) daily during 14 consecutive days; the paper does not state how the consumption of tonic was spread out over the day. The more extensive investigational report of this study, which was available to the SCF in 1988, could not be retrieved by the Panel. The authors concluded that, under the conditions of the studies, the consumption of tonic water sufficient to provide 100 or 120 mg quinine hydrochloride daily for 14 days was without visual, audiometric or other effects.

Another very limited study which was available to the 1988 committee assessment (Zajtchuk et al., 1984), concerned 13 active duty military subjects (no further details provided) who drank 822 or 1 644 ml of tonic water containing 52.5 or 105 mg quinine, respectively, over a three-hour period daily for 14 days. At the low intake no changes in a number of audiometric or electronystagmographic (ENG) parameters were detected; however, three of the four subjects in the high-dose group were found to exhibit non-localising positional abnormalities on at least one ENG.

A several-fold higher intake of quinine occurs during *medical prescription* use of quinine (see below); the side effects reported (detailed below) therefore reflect effects at higher exposure than the above study by Drewitt et al. (1993); moreover, in the prescription use of quinine the whole dose is consumed at one time, giving rise to high-peak plasma levels, while in the Drewitt et al. (1993) study it was divided into four equal portions per day. The intake pattern was more spread out, with much lower plasma peak levels, and probably reflects the consumer exposure to quinine more realistically.

Purified quinine salts have been used as medicinal drugs against malaria since the 19th century. Therefore, a lot of data are available on effects in humans. Currently, the only registered indication for quinine is against certain forms of malaria. Because quinine has neuromuscular-blocking activity, in several countries it is widely used off-label for treatment of nocturnal cramps, despite limited evidence of efficacy; it is not a registered indication (see, for example, FDA (2009)). The off-label use against leg cramp is 200–300 mg per day at night (Man-Son-Hing and Wells, 1995); in the USA this dose will be 324 mg because that is the minimum dose available for Qualaquin (quinine sulphate).

The following information on side effects of quinine is was retrieved mainly from the FDA (2011); similar descriptions are available from the Martindale Pharmacopoeia and regulatory authorities of various European countries. The World Health Organization (WHO) provides no information with respect to effects that might occur after long-term administration of quinine to humans (WHO, 2015). The European Medicines Agency (EMA) was contacted and confirmed that quinine is not used prophylactically against malaria, and the use against restless legs is off-label in most EU countries. According to Medicines and Health products Regulatory Agency (MHRA, www.gov.uk/drug-safety-update/quinine-not-to-be-used-routinely-for-nocturnal-leg-cramps), the recommended doses used for the second-line use of quinine (in the United Kingdom) range from 200 to 300 mg per day. Although these dose levels are generally well-tolerated, side effects, such as those reported for malaria treatment, may occur.

The suggested dose of quinine for treatment of malaria in adults is 3 times 500 mg quinine (equivalents) per day for 3–10 days; in children 3 times 8.2 milligram quinine equivalents/kg/day is

advised, also for 3–10 days (WHO, 2015). Under those conditions the following side effects may occur: in almost all patients, to some degree, cinchonism (usually after the third day of treatment: vertigo, nausea, tinnitus, hearing impairment, tremors, headache, vision disturbances); more severe symptoms of cinchonism are vomiting, abdominal pain, diarrhoea, deafness, blindness and heart disturbances. In general, these symptoms of cinchonism are rapidly reversible and resolve with discontinuation of quinine.

Further, many side effects are reported which are considered uncommon, but of which the actual incidence is unknown, such as haematological, cardiovascular, metabolic (hypoglycaemia), renal and hearing or vision disturbances. Rare side effects include various allergic (idiosyncratic) reactions (such as pruritus, urticaria, dyspnoea, asthmatic symptoms, thrombocytopenia), acute intravascular haemolysis, haemolytic–uraemic syndrome, kidney failure, heart rhythm disturbances and angina complaints.

Taylor and White (2004) reviewed many of the clinical quinine side effects in detail, for both of the regular clinical doses, as well as after overdosing; much higher than the proposed use level as flavouring agent, as indicated above (Taylor and White, 2004).

Hypoglycaemia: Quinine stimulates release of insulin from the pancreas, and patients; especially pregnant women, may experience clinically significant hypoglycaemia. It affects up to 10 % of patients with severe malaria given quinine; profound hypoglycaemia occurs in 50 % of pregnant women with severe malaria, treated with quinine at the regular high dose schedule specified above.

Eye and auditory toxicity: These types of toxicity are transient and reversible, except in overdosed patients. Effects of quinine on the human auditory system in otologically normal volunteers have been extensively studied. For instance, Berninger et al. (1998) studied the effects of 15 mg/kg body weight (bw) quinine hydrochloride (approximately 1 000 mg per person) in 21- to 40-year old volunteers; hearing loss in several parameters was observed, which was completely reversible (Berninger et al., 1998). Studies in, for example, guinea pigs (Zheng et al., 2001) on the mechanisms related to auditory toxicity indicate that primary effects are on the cochlear spiral ganglion neurons and/or their presynaptic process. Similarly, the visual effects of quinine have been studied in animal experiments. Quinine hydrochloride (100 and 300 mg/kg orally) caused a temporary attenuation of visual acuity in rats when tested 120 minutes after administration, which appears to correlate with the onset of human cinchonism symptoms, which commonly appear within 1–3 hours after ingestion (Carlsson and Swedberg, 2010).

Cardiac effects: These effects are particularly important during intravenous injection of quinine; after oral dosing they seem to be rare.

Haematological reactions: Rare cases of idiosyncratic thrombocytopenia, which may be fatal, have been reported, even when used against restless legs (FDA, 2009), presumably at the dose of 324 mg (unless overdose occurred). In addition, leucopenia and acute intravascular haemolysis (“blackwater fever”) have been reported.

Hypersensitivity: Quinine has a long history of use as a bitter agent in drinks. However, there are reports (BfR, 2008; FDA, 2011) on hypersensitive individuals. No prevalence data could be found in recent literature; however, the incidence of this hypersensitivity seems to be rare.

Various idiosyncratic skin reactions are associated with quinine, such as pruritus, skin flushing and urticarial (Gonzales et al., 2002). Hypersensitivity may also lead to other severe reactions (e.g. thrombocytopenia, haemolytic–uraemic syndrome or acute renal failure) (Gottschall et al., 1994; Howard et al., 2003) even at low level intake, such as a single glass of bitter lemon containing 20 mg/l quinine (Murray et al., 1979).

These side effects have led to contraindications or warnings in patients with tinnitus, optic neuritis, glucose-6-phosphate dehydrogenase deficiency, hypersensitivity reactions, a prolonged QT interval, atrium fibrillation or myasthenia gravis. (CBG-MEB, 2015; MHRA, 2015)

No data on carcinogenicity of quinine in laboratory animals and humans have been identified.

8.3. Developmental/reproductive toxicity studies

Although at high doses of quinine there are some reports on abortion in pregnant women, as well as eye defects and hearing loss in newborns, there is no evidence of an increased risk for such effects in pregnant women with the use of the standard dosage of quinine (see above) for treatment of acute malaria (Schaefer, 2001). This is confirmed by McGready et al. (2005) in a study in 81 women in the second or third trimester of pregnancy with malaria, and in an investigation on treatment in the first trimester (McGready et al., 2011).

8.4. Genotoxicity studies

The SCF (1988) assessed data on genotoxicity available at that time. The Ames test with *Salmonella* strains TA98, TA100, TA1535, TA1537 and TA1538, as well as a micronucleus test, did not show any genotoxicity. The SCF concluded that the large number of mutagenicity tests *in vitro* and *in vivo* confirmed the absence of genotoxic activity of quinine; however, the reports on which this conclusion was based could not be retrieved by the Panel.

The following genotoxicity data have been made available to the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) by request to Industry, and by a survey of the open literature. Data on deoxyquinine were also included, since this substance may be considered as supporting substance.

8.4.1. *In vitro*

8.4.1.1. Quinine dihydrochloride

Quinine dihydrochloride, along with a number of other chemicals, was tested in bacterial reverse mutation tests with *Salmonella typhimurium* (*S. typhimurium)* strains TA98, TA100, TA1535, TA1537 and TA1538 using the plate-incorporation methodology and *Escherichia coli* (strain K12/343/113), both in the absence and presence of metabolic activation (King et al., 1979). The material tested was purchased from EGA-Chemie GmbH and Co. KG, Steinheim/Albuch, Germany, exhibiting the correct melting point and elemental analysis and was used without further purification. Under "Materials and methods" it is stated that at least five concentrations were tested, usually up to 3.6 mg/plate. King et al. (1979) report that quinine dihydrochloride induced, in strain TA98, a concentration-dependent increase (up to 8.7 µmol/plate; at higher concentrations a decrease was observed) in the number of revertants in the presence of S9-mix, but not in the absence of metabolic activation. Neither raw data nor means with standard deviation (SD) are reported. Results of TA98 were presented in a figure stating that the values represent the average of four plates. In total, seven concentrations were tested, a clear dose response with a six-fold increase compared with negative control could be deduced; the two highest concentrations showed cytotoxicity (decrease in the number of revertants). The Panel considered that the methods and data are not sufficiently documented (no raw data, no means with SD and no historical control data) and, accordingly, the validity of this study is considered to be limited.

8.4.1.2. Quinine hydrochloride [FL-no: 14.011]

Quinine hydrochloride was tested in two separate assays (in a plate incorporation and a pre-incubation test) with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, with and without S9-mix (Münzner and Renner, 1983). The test material was purchased from Merck (purity not specified). The test concentrations were 0.05, 0.1, 0.5, 1.0, 2.5 and 5 mg/plate. In the plate incorporation assay, evidence of toxicity was observed at concentrations >1 mg/plate, which was diminished in the presence of S9-mix. In this study, the results of the plate incorporation test were adequately reported

(means and SDs) while the results of the pre-incorporation test were not reported in detail. According to the description in the materials and methods section, a positive control was performed, but the data were not shown. Under all conditions tested, quinine hydrochloride did not induce any increase in revertants. However, the Panel considered that the validity of this study is limited because no data on the positive controls were reported.

Quinine hydrochloride was tested for genotoxicity in three experimental setups using *Salmonella* strains TA97 and TA102 and *E. coli* strains WP2, WP2 trp-uvrA, WP6 trp-polyA1, WP67 trp-uvrA and polyA1 (Obaseiki-Ebor and Obasi, 1987).

- A spot-test was applied; however, the spot test is not a standard assay and is not used for regulatory purposes.
- A plate incorporation assay including a non-standard bacterial strain (*E. coli* WP6 trp-polyA1) was applied. The low- and mid-concentrations (25 and 50 µg/plate) induced a dose-dependent increase of WP6 trp-polyA1 revertants, the highest concentration (100 µg/plate) revealed to be toxic (decrease in the number of revertants) while no revertants were observed with the negative control. However, the Panel noted that no historical control data were available and that the study was only poorly reported.
- A fluctuation test with WP6 revealed positive tubes at all concentrations tested but no dose-dependency.

Overall, the Panel considered that the results of the plate incorporation test are of limited validity and the results observed in the spot test and fluctuation test are of limited relevance as these tests are not listed among those recommended for regulatory purposes (EFSA, 2011).

8.4.1.3. Quinine monohydrochloride dihydrate [FL-no. 14.155]

Quinine monohydrochloride dihydrate [FL-no. 14.155] was tested in a bacterial gene mutation assay in five histidine-requiring strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102), both in the absence and presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S9-mix) (Bowen, 2014). The study was performed according to the Organisation for Economic Co-operation and Development (OECD) Guideline 471, and in compliance with GLP. Two separate experiments were performed. Purified water was used as solvent. In the first experiment, quinine monohydrochloride dihydrate was tested in a plate incorporation assay at seven concentrations from 5 to 5 000 µg/plate. In the second experiment, which included a pre-incorporation step, narrowed concentration intervals were employed covering eight concentrations in the range from 40 to 5 000 µg/plate. In experiment 1, toxicity was observed at 1 600 µg/plate and above in strain TA102 in the absence and presence of metabolic activation, and at 5 000 µg/plate in strains TA98, TA100, TA1535 and TA1537 in the absence of S9-mix and in strains TA100 and TA1537 in the presence of S9. In experiment 2, toxicity was observed in all strains in the presence and absence of metabolic activation at lower concentrations than in experiment 1. According to the study report, the test article was completely soluble in the aqueous assay system at all concentrations applied. Quinine monohydrochloride dihydrate did not induce mutations in this study.

Quinine monohydrochloride dihydrate [FL-no: 14.155] was tested in an *in vitro* micronucleus assay in human lymphocytes, both in the absence and presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S9) (Watters, 2014). The study was performed according to OECD Guideline 487, and in compliance with GLP. Duplicate human lymphocyte cultures prepared from the pooled blood of two female donors were used in a single experiment. The concentrations applied in the main experiment were determined based on a cytotoxicity range-finder experiment in which the replication index was used as an indicator for cytotoxicity and in which quinine monohydrochloride dehydrate was investigated at 12 concentrations between 14.4 and 3 969 µg/ml. It induced significant cytotoxicity at concentrations of 514.4 µg/ml and greater in the absence and presence of S9 (3 + 21 hour treatments), and at concentrations of 185.2 µg/ml and greater in the

absence of S9 (24 + 0 hour treatment). Accordingly, the substance was tested in the main experiment at concentrations of 100, 250, 350 and 400 µg/ml in the absence of S9, at 200, 325, 350 and 400 µg/ml in the presence of S9 (3 + 21 hour treatments) and at 20, 60 and 120 µg/ml without S9 (24 + 0 hour treatment). Purified water was used as solvent. At higher concentrations, cytotoxicity was observed. The treatments were conducted 48 hours following mitogen stimulation by phytohaemagglutinin. The frequencies resulting from the treatment of cells with quinine monohydrochloride dehydrate were similar to those observed in concurrent vehicle controls and were within historical control ranges. Thus, quinine monohydrochloride dehydrate did not induce micronuclei in this study.

8.4.1.4. Deoxyquinine

Deoxyquinine (source and purity of the test substance not reported) was tested in two separate experiments with *Salmonella typhimurium* strains TA98, TA100 and TA1537 (Richold and Jones, 1980). In the first experiment, concentrations up to 3 000 µg/plate were applied, both in the absence and presence of metabolic activation. Evidence of toxicity was observed for TA1537 at all concentrations and for TA98 and TA100 at the highest concentration. No increase in revertants was observed; the positive control demonstrated the correct/reliable performance of the assay. The repeat test was performed without metabolic activation at concentrations up to 375 µg/plate, deoxyquinine, again, did not increase the number of revertants in TA1537, TA98 and TA100. The Panel considered this report to be of limited validity since it was not fully in compliance with current OECD Guideline 471 (not all strains used as recommended).

8.4.2. *In vivo*

The *in vivo* studies on quinine dihydrochloride and quinine hydrochloride were performed by King et al. (1979) and Münzner and Renner (1983) and published along with data on *in vitro* assays described above.

Quinine dihydrochloride was reported to be negative in a mouse bone marrow micronucleus test (King et al., 1979). According to the methods section, three dose levels were administered to four mice/group, twice at 24 hours apart, either intraperitoneally or orally (gavage), but results were reported for only one dose level (2 × 0.5 mmol/kg). The mice were sacrificed six hours (instead of 18 to 24 hours, as recommended by OECD Guideline 474) after the last dosing and 1 000 polychromatic erythrocytes (PCEs)/mouse were scored. However, the PCE/normochromatic erythrocyte (NCE) ratio was not reported and thus it is not clear if the test substance reached the bone marrow. The Panel considered that the validity of this study is insufficient.

Quinine hydrochloride [FL-no: 14.011] was tested for the induction of chromosomal aberrations and micronuclei using a single oral dose of 110 mg/kg bw administered to mice (C3H, NMRI) and hamsters (Münzner and Renner, 1983). No significant increase in the frequency of chromosomal aberrations was found (sampling at 24 hours after dosing plus two hours colchicine, 300 metaphases/mouse scored). Likewise, at 30 hours after dosing no increase in micronuclei was found (1 000 PCE/mouse scored) in NMRI mice and hamsters. In contrast, in C3H mice, the frequency of micronuclei observed after administration of quinine hydrochloride was statistically significantly higher than the frequency observed in control mice; however, the increase was only slight (less than two-fold compared with the control group) and its relevance cannot be evaluated since historical control data were not reported and additional doses would have been required in order to evaluate a potential dose–response relationship. In addition, the study exhibits further limitations. In the chromosomal aberration test, only one dose and one time point were investigated and in the micronucleus test the PCE/NCE ratio was not reported, and thus it is not clear if the test substance reached the bone marrow of NMRI mice and hamsters. Overall, the reliability of this study is considered insufficient.

Further studies on genotoxicity of quinine comprise a sister chromatid exchange (SCE) assay in three mice strains and in hamsters (Münzner and Renner, 1983) as well as a host-mediated assay in mice and a sex-linked recessive lethal test in *Drosophila* (King et al., 1979).

Quinine dihydrochloride induced dose-dependent increases of SCEs in bone marrow of C3H and C57Bl mice treated by gavage with doses of 55, 75 or 110 mg/kg bw (Münzner and Renner, 1983). The frequencies of SCEs were statistically significantly increased at the high dose in C3H mice and at medium and high doses in C57B1 mice compared with control mice, respectively. However, the effects were weak (the increase was less than 1.3-fold in C3H mice and less than 1.4-fold in C57BI mice). NMRI mice and hamsters were treated with a dose of 110 mg/kg bw only, resulting in a statistically significant increase in SCEs in NMRI mice but not in hamsters. In addition, this effect was very weak (less than 1.2-fold compared with the control group). SCE is considered as a genetic endpoint of limited relevance. Quinine hydrochloride was negative in the host-mediated assay with NMRI mice and in a sex-linked recessive lethal assay with *Drosophila* (King et al., 1979). Both assays are not listed among those recommended for regulatory purposes (EFSA, 2011). Therefore, the Panel considered these assays to be of limited relevance.

8.4.3. Conclusion on genotoxicity

On the basis of the genotoxicity data available on the quinine salts it is concluded that there is no concern with respect to genotoxicity for the candidate substances, when used as flavouring substances.

Data on genotoxicity are summarised in Table 5 and 6.

9. Safety evaluation of quinine for use as a food flavouring agent

Considering the absence of a genotoxic potential, the Panel considered it appropriate that the safety of quinine for use as a flavouring agent can be assessed following a threshold approach. From its use as an anti-malaria agent, it is well known that, at therapeutic doses, quinine may elicit a plethora of adverse effects. These side effects observed during prescription use of quinine, occur at a much higher dose than that intended for use as flavouring substance. Moreover, each clinical dose is taken as a capsule, leading to higher peak concentrations than the one expected from food intake. From its use as a flavouring substance in food, it is known that hypersensitive people may also show adverse effects after consumption of quinine-containing drinks.

From an adequate 21-day double-blinded cross-over design volunteer study in humans, a NOAEL of 72 mg quinine equivalents/person/day could be derived. Based on these human data, the Panel concluded that the quinine salts are not expected to be of safety concern at their estimated levels of intake as flavouring substances. An adequate margin of safety of 100 for the sum of quinine equivalents from all three salts can be calculated based on the comparison of the NOAEL for quinine equivalents of 72 mg/person/day from a study in humans, with the estimated daily *per capita* intake (i.e. the MSDI) of 746 µg quinine equivalents/*capita*/day. Compared with the highest mTAMDI, 29 100 µg quinine equivalents per person per day, the margin of safety is 2.5. The Panel also noted that this mTAMDI is approximately three-fold below the worst-case exposure scenario of 100 mg/person/day dose which was assumed by the BfR.

The Panel recognised that the adverse effects reported for quinine are related to short-term exposure therefore the abovementioned 21-day study is sufficient to cover these effects.

The Panel noted that there is a legal obligation for quinine-containing foods to be labelled as such.

CONCLUSIONS

Compared with FGE.35, which consisted of three candidate substances, all being salts of quinine from the priority list, this FGE.35Rev1 includes specification data on quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155], new intake data on all three candidate substances, as well as toxicological and new genotoxicity data on quinine hydrochloride [FL-no: 14.011] and two structurally related quinine salts.

The quinine component is the (−)-isomer, which has (8*S*,9*R*)-configuration.

All three substances are classified into structural class III and do not naturally occur in food.

Because the three candidate substances are water-soluble salts of the same flavouring component, quinine, and because they are expected to replace each other in beverages, the Panel decided to carry out the safety assessment on the basis of exposure to quinine equivalents.

On the basis of the genotoxicity data available on the quinine salts, it is concluded that there is no concern with respect to genotoxicity for the candidate substances, when used as flavouring substances.

The Panel considered a well conducted 21-day study in humans, with much higher levels of exposure to quinine than those resulting from its use as flavouring substance at levels reported in this FGE.35Rev1 (i.e. MSDI of 745 µg/*capita*/day (expressed as quinine equivalents) or a highest mTAMDI of 29 100 µg quinine equivalents/person/day for [FL-no: 14.011]), providing a NOAEL of 72 mg quinine equivalents/person/day. Because of the availability of this study and the knowledge of quinine toxicity following its use as an anti-malarial agent, the Panel decided that the Procedure for the evaluation of Flavouring substances, as laid down in Commission Regulation (EC) No 1565/2000, is not applicable. The Panel considered the use of quinine at levels of exposures, as indicated by the mTAMDI, not of safety concern. The mTAMDI is expected to reliably reflect the use of quinine because its consumption is limited to only two food categories: alcoholic and non-alcoholic beverages.

These exposure levels are equivalent to a daily consumption of approximately 300 ml of non-alcoholic beverages containing quinine at the maximum permitted level of 100 mg/l. The margin of safety is approximately 100 for the MSDI and 2.5 for the mTAMDI.

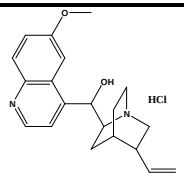
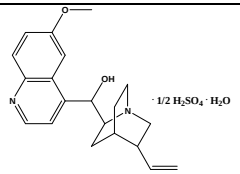
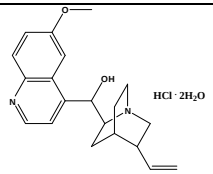
The Panel noted that a very high intake (e.g. more than 1 litre) of non-alcoholic beverages containing quinine or its salts at the maximum permitted level could result in adverse health effects in humans.

In order to determine whether the conclusion for the candidate substances can be applied to the material of commerce, it is necessary to consider the available specifications. Specifications including purity criteria and identity for the materials of commerce have been provided for all three candidate substances.

Accordingly, the three flavouring substances, quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155] would present no safety concern at the levels of intake estimated on the basis of the MSDI or mTAMDI approach. In this evaluation, the Panel addressed only those food categories (14.1 and 14.2) in which the use of quinine is permitted according to Annex I of Commission Regulation (EC) No 1334/2008. Therefore, this evaluation is applicable for only the use of quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155] in alcoholic and non-alcoholic beverages. Considering the occurrence of hypersensitivity against quinine in the human population, the Panel would support continuation of the legal requirement for labelling of quinine-flavoured foods.

SUMMARY OF SAFETY EVALUATION

Table 4: Summary of Safety Evaluation

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
14.011	Quinine hydrochloride		790	Class III Not taken through the procedure		f	
14.152	Quinine sulphate		0.13	Class III Not taken through the procedure		f	
14.155	Quinine monohydrochloride dihydrate		45	Class III Not taken through the procedure		f	

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

GENOTOXICITY DATA

Table 5: Genotoxicity (*in vitro*)

Chemical Name [FL-no][(a)]	Test System	Test Object	Concentration	Result	Reference	Comments
Quinine dihydrochloride	Ames test Plate incorporation	1) *S. typhimurium* TA100, TA1535, TA1537, TA1538 *E. coli* K12/343/113 2) *S. typhimurium* TA98,	Five concentrations up to 3600 µg/plate	1) Negative[(b,c)] 2) Positive[(c)]	(King et al., 1979)	The validity of this study is considered to be limited as the methods and data are not sufficiently documented (no raw data, no means with SD and no historical control data).
Quinine hydrochloride [14.011]	Ames test Plate incorporation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0, 50, 100, 500, 1000, 2.500, 5000 µg/plate	Negative[(b,c)]	(Münzner and Renner, 1983)	Evidence of toxicity was observed at concentrations above 1000 µg/plate, which was deminished in the presence of S9-mix. The validity of this study is considered to be limited due to the fact that no data on the positive controls were reported.
	Ames test preincubation method	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0, 50, 100, 500, 1.000, 2.500, 5000 µg/plate	Negative[(b,c)]	(Münzner and Renner, 1983)	The validity of this study is considered to be limited due to the fact that no data on the positive controls were reported.
	Ames test Plate incorporation	1) *S. typhimurium* TA97, TA102 *E. coli* WP2 trp; WP2trp, uvrA; *E. coli* WP67 trp, uvrA, polyA1 2) *E. coli* WP6 trp, polyA1;	10–1000 µg/ml	1) Negative[(b)] 2) Positive[(b)]	(Obaseiki-Ebor and Obasi, 1987)	The study is poorly reported. A spot test was also applied, but it is not a standard assay and is not used for regulatory purposes. A fluctuation-test with WP6 revealed positive tubes at all concentrations tested but no dose-dependency were seen. Overall the Panel considered that the results of the plate incorporation test are of limited validity and the results observed in the spot test and fluctuation test are of limited relevance.

Table 5: Genotoxicity (*in vitro*)

Chemical Name [FL-no][(a)]	Test System	Test Object	Concentration	Result	Reference	Comments
Quinine monohydrochloride [14.015]	Ames test Plate incorporation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	5–5000 µg/plate	Negative[(b,c)]	(Bowen, 2014)	Evidence of toxicity was observed at 1600 µg/plate and above for TA 102 in presence and absence of S9-mix and at 5000 µg/plate in TA98, TA100, TA1535 and TA1537 in absence of S9-mix and in TA100 and TA1537 in presence of S9-mix. The study has been performed according to OECD guidelines and according to GLP. This study is considered to be valid.
	Ames test preincubation method	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	40–5000 µg/plate	Negative[(b,c)]	(Bowen, 2014)	Evidence of toxicity was observed starting from 1250 µg/plate and above in all strains and both in presence and absence of S9-mix The study has been performed according to OECD guidelines and according to GLP. This study is considered to be valid.
	Micronucleus test	Human lymphocytes	100, 250, 350, and 400 µg/ml[(b,d)] 200, 325, 350, and 400 µg/ml[(c,d)] 20, 60 and 120 µg/ml[(b,e)]	Negative	(Watters, 2014)	Cytotoxicity has been observed at the highest concentrations. The study has been performed according to OECD guidelines and according to GLP. This study is considered to be valid.
(Deoxyquinine)	Ames test	*S. typhimurium* TA98, TA100, TA1537	375, 750, 1500, 3000 µg/plate	Negative[(b,c)]	(Richold and Jones, 1980)	Evidence of toxicity was observed for TA1537 at all concentrations and for TA98 and TA100 at the top concentration. No increase in revertants was observed, the positive control demonstrated the correct/reliable performance of the assay. The study is considerd of limited validity since it is not fully in compliance with OECD guidelines (not all strains as recommended).

Table 5: Genotoxicity (*in vitro*)

Chemical Name [FL-no][(a)]	Test System	Test Object	Concentration	Result	Reference	Comments
	Ames test	*S. typhimurium* TA98, TA100, TA1537	0, 23.43, 93.75, 375 µg/plate	Negative[(b)]	(Richold and Jones, 1980)	The repeat test was performed without metabolic activation at concentrations up to 375 µg/plate, deoxyquinine again did not increase the number of revertants in TA98, TA100, TA1537. The Panel considered this report to be of limited validity since it is not fully in compliance with OECD guidelines (not all strains as recommended).

(a): Supporting substances are listed in brackets.
(b): Without metabolic activation.
(c): With metabolic activation.
(d): 3+21 hours treatment.
(e): 24 hours treatment.

Table 6: Genotoxicity (*in vivo*)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Refence	Comments
Quinine dihydrochloride	*In vivo* Micronucleus test	Mouse (NMRI) bone marrow (male and female mice)	Intraperitoneal injection/ gavage	3 doses, but only one specified: 2x0.5mM/kg	Negative	(King et al., 1979)	The mice were sacrificed 6 hrs (instead of 18 to 24 hours as recommended by OECD guideline 474) after the last dose 1000 PCE/mouse were scored. However, the PCE/NCE ratio was not reported and thus, it is not clear if the test substance reached the bone marrow. The validity of the *in vivo*-part of study by King et al. is insufficient.
Quinine hydrochloride [14.011]	*In vivo* Chromosomal aberration assay	Mouse (C3H, NMRI) Hamster	Gavage	110 mg/kg bw, single dose	Negative	(Münzner and Renner, 1983)	The data were poorly reported and the study is considered of limited validity (only one dose and one time point was investigated).
	In vivo Micronucleus test	Mouse (C3H, NMRI) Hamster	Gavage	110 mg/kg bw, single dose	NMRI mice, hamster: Negative C3H mice: Positive	(Münzner and Renner, 1983)	The data were poorly reported and the study is considered of limited validity (the PCE/NCE ratio was not reported and thus, it is not clear if the test substance reached the bone marrow of NMRI mice and hamsters).

DOCUMENTATION PROVIDED TO EFSA

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Appendix A. Use levels/mTAMDI

A.1 Normal and maximum use levels

For each of the 18 Food categories (Table 7) in which the candidate substances are used, the Flavour Industry reports a "normal use level" and a "maximum use level" (EC, 2000a). According to the Industry the "normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004).

Table 7: Food categories according to Commission Regulation (EC) No 1565/2000

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

The “normal and maximum use levels” are provided by the Flavour Industry (Flavour Industry, 2011) for all the candidate substances in the present flavouring group (Table 8).

Table 8: Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.35Rev1 (Flavour Industry, 2011)

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**
14.011	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-
	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-
14.152	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-
	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-
14.155	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-
	10	-	10	-	-	40	-	20	-	-	-	-	-	-	100	100	-	-

A.2 mTAMDI calculations

The method for calculation of mTAMDI values is based on the approach used by SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amount of flavourable foods and beverages listed in Table 9. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

Table 9: Table Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995).

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

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 and reported by the Flavour Industry in the following way (see Table 10):

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

Table 10: Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995).

	Food categories according to Commission Regulation 1565/2000	Distribution of the seven SCF food categories		
Key	**Food category**	**Food**	**Beverages**	**Exceptions**
01.0	Dairy products, excluding products of category 02.0	Food		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03.0	Edible ices, including sherbet and sorbet	Food		
04.1	Processed fruit	Food		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Food		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07.0	Bakery wares	Food		

Table 10: Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995).

	Food categories according to Commission Regulation 1565/2000	**Distribution of the seven SCF food categories**		
Key	**Food category**	**Food**	**Beverages**	**Exceptions**
08.0	Meat and meat products, including poultry and game	Food		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10.0	Eggs and egg products	Food		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Food		
14.1	Non-alcoholic ("soft") beverages, excl. dairy products		Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts			Exception c
15.0	Ready-to-eat savouries			Exception b
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0	Food		

The mTAMDI values (see Table 11) are presented for all candidate substances in the present flavouring group (Flavour Industry, 2011). The mTAMDI values are given only for the highest reported normal use levels (see Table 11).

Table 11: Estimated intakes based on the mTAMDI approach

FL-no	**EU Register name**	**mTAMDI (µg/person/day)**	**Structural class**	**Threshold of concern (µg/person/day)**
14.011	Quinine hydrochloride	38000	Class III	90
14.152	Quinine sulphate	38000	Class III	90
14.155	Quinine monohydrochloride dihydrate	38000	Class III	90

Appendix B. Metabolism

B.1 Introduction

The following information on the metabolism of quinine is mainly retrieved from the FDA (2011); similar descriptions are available from Martindale Pharmacopoeia and regulatory authorities of various European countries.

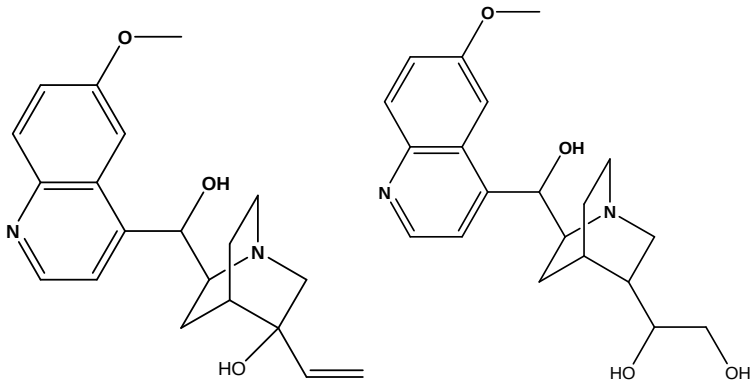
B.2 Absorption, metabolism and elimination

Absorption of quinine is rapid and almost complete; oral availability is 76–88 %. Food delays the absorption somewhat compared with the fasted state, but does not affect the Area Under the Curve (AUC) of the quinine plasma concentration. In healthy adults the volume of distribution (Vd/f) ranges from 2.5–7.1 l/kg. Protein binding ranges from 69–92 %. Quinine penetrates relatively poorly into brain tissue, having a cerebrospinal fluid concentration of approximately 2–7 % of the plasma concentration. It is excreted in breast milk and present in placental cord blood at approximately 30 % of the maternal plasma concentration. Half-life of elimination is 9.7–12.5 hours in healthy adults.

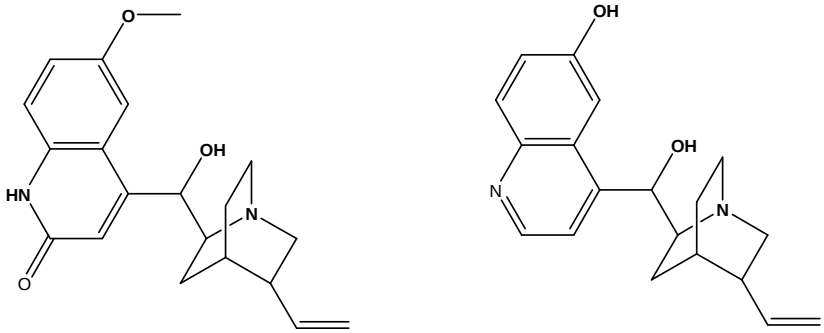
The pharmacokinetics in children are very similar to those in adults. In elderly subjects (65–78 years old) the clearance of quinine is decreased (half-life of elimination of 18.4 hours compared with 10.5 hours in 20–35-year-old controls). In patients with mild to moderate hepatic impairment (Child–Pugh B) there is a 55 % increased AUC of quinine and an increased half-life of elimination. In subjects with severe chronic renal impairment the half-life is prolonged to 26 hours.

B.3 Metabolism

Metabolism occurs predominately in the liver, mainly by cytochrome P450 (CYP) 3A4; other CYPs may also contribute. The major metabolite is 3-hydroxyquinine; further, 2′-quinone, *O*-desmethylquinine and 10,11-dihydroxydihydroquinine are formed. Six secondary metabolites are formed by further metabolism (Bannon et al., 1998). The metabolites, as well as 20 % of unchanged quinine, are excreted in urine (see Figure 1).



3-Hydroxyquinine 10,11-dihydroxydihydroquinine



2′-Quinone *O*-desmethylquinine

Figure 1: Structures of the major metabolites of quinine (Bannon et al., 1998)

B.4 Conclusion

This group of flavouring substances consists of three candidate substances, all of which are salts of quinine: quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155]. They are readily water soluble, leading to freely dissolved quinine.

Data on absorption, distribution and elimination of quinine in humans are available from the open literature. The data indicate that the substances in this group are well absorbed, mainly from the intestinal lumen, and are rapidly excreted. Major metabolites have been identified. However, the information on the metabolism of the substances in this flavouring group does not allow the conclusion that these substances will be metabolised to innocuous products

Appendix C. Evaluation/regulation status

Quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152] and quinine monohydrochloride dihydrate [FL-no: 14.155].

SCF report of the Scientific Committee for Food on quinine (opinion expressed 19 February 1988)

"The SCF acknowledges that it has been provided with comprehensive additional information and new studies in response to its requests.

The Committee is now assured that no adverse reproductive or teratological effects will result from the use of quinine in bitter drinks.

The Committee has also been provided with information on actual and potential intakes of quinine from bitter soft drinks at a European level. The estimated actual intake in European countries is, on average, of the order of 0.26 mg/person/day, and for regular consumers of bitter drinks it is unlikely that the mean daily intake will exceed 5 mg quinine per person/day. This information is reassuring for the Committee and it has noted that intake appears to be restricted to the adult population.

Military jet-pilots consuming 105 mg quinine daily showed, under extremely strenuous conditions, mild adverse effects, but these effects are not considered relevant in the context of the use of quinine as a food additive. For human volunteers under normal conditions 120 mg/person/day gave no effects. This should not be considered in relation to the estimated maximum daily intake of 5 mg/person/day in Member states.

Some individuals are hypersensitive to quinine, as occurs with other food components and food additives. These persons should be informed by the specific mention of the presence of quinine on the label.

The Committee sees no objections from a toxicological point of view to the continued use at present levels (up to max. 100 mg/l) of quinine in bitter drinks."

The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) evaluation of quinine (JECFA, 1993)

"Quinine was last reviewed by the Committee at its thirty-ninth meeting, when a clear No Observed Effect Level (NOEL) with respect to ocular effects in humans of 80 mg of anhydrous quinine hydrochloride per day (equivalent to 72 mg of free base) was observed. At that time, the Committee withdrew the previously established temporary Acceptable Daily Intake (ADI) of 0–0.9 mg of quinine per kg body weight per day and concluded that current levels of use in soft drinks, which the Committee was informed were up to 75 mg/l (as quinine base), were not of toxicological concern.

At its present meeting, the Committee re-assessed the toxicological information in the light of new data on levels of quinine in beverages. The Committee concluded that current levels of use up to 100 mg/l (as quinine base) in soft drinks were not of toxicological concern. The contribution of other uses of quinine in food and alcoholic beverages to daily intakes was considered to be negligible.

The Committee again noted that certain consumers show an idiosyncratic hyper-reactivity to quinine, and reiterated its recommendation that the consumer should be informed by appropriate means of the presence of quinine in foods and beverages in which it is used.

A toxicological monograph was not prepared. The existing specifications for quinine hydrochloride and quinine sulfate were revised."

EU Regulation (Commission Directive 2002/67/EC)

There is an amendment (Commission Directive 2002/67/EC (EC, 2002)) to the EC labelling directive (European Council Directive 2000/13/EC): By derogation from Article 6(6), second subparagraph, third indent, of Directive 2000/13/EC, quinine and/or caffeine used as a flavouring in the production or preparation of a foodstuff must be mentioned by name in the list of ingredients indicated in Article 3(1)(2), of Directive 2000/13/EC, immediately after the term "flavouring" (EC, 2000b).

German Federal Institute for risk Assessment (BfR): "Quinine-containing beverages may cause health problems" (BfR, 2008)

Summary

"Quinine is a bitter-tasting, crystalline white powder. It is obtained from the bark of the cinchona tree and belongs to the group of alkaloids. In medicine quinine is used to treat malaria and nocturnal leg cramps. In the food sector, quinine is used as a flavouring mainly in beverages like bitter lemon and tonic water.

When larger amounts of quinine are consumed, it can constitute a health problem for some consumer groups. BfR sees risks in particular for quinine intakes during pregnancy. For instance, a newborn baby, whose mother had drunk more than 1 litre tonic water a day in the weeks up to its birth, suffered health disorders. Based on existing regulations in the medicinal product sector, BfR, therefore, advises pregnant women against drinking quinine-containing beverages on precautionary grounds. People who have been advised against taking quinine, cinchona bark or their preparations by their doctors because of their clinical pictures should not consume any quinine-containing soft drinks either. This applies, for instance, to people who suffer from tinnitus, pre-existing damage to the optic nerve, haemolytic anaemia or who are hypersensitive to quinine or cinchona alkaloids. Patients with cardiac arrhythmia and people who take medicine that interacts with quinine, should only drink quinine-containing soft drinks after consulting their doctors. This applies in particular to medications which inhibit blood coagulation. At higher levels of tonic water consumption, it may be necessary to reduce their therapeutic dose.

Already today quinine must be mentioned by name in the list of ingredients of quinine-containing products. BfR also believes that there is a need for information which attracts the attention more particularly of pregnant women and other risk groups to possible health impairments. Motor vehicle drivers should be informed that larger amounts of quinine-containing bitter beverages can cause visual disturbances. BfR recommends raising awareness about the possible health risks from quinine to consumers. Specific information should be provided about the symptoms of quinine hypersensitivity and cinchonism (typical adverse reactions to quinine). Consumers should be advised to immediately stop their quinine intake if these symptoms occur, and to consult a doctor.

BfR recommends that the health assessment of quinine by the Scientific Committee on Food from 1988 should be updated.

BfR is of the opinion that the problems of quinine-containing bitter soft drinks underline the importance of the systematic recording of adverse reactions that occur in conjunction with the consumption of foods. The Institute, therefore, explicitly supports the setting up of a central reporting office."

ABBREVIATIONS

ADI	Acceptable Daily Intake
AUC	area under the curve
BfR	German Federal Institute for risk Assessment
bw	body weight
CAS	Chemical Abstracts Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EC	European Commission
ECG	electrocardiogram
EFFA	European Flavour and Fragrance Association
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
ID	Identity
IOFI	International Organization of the Flavor Industry
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
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
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PCE	polychromatic erythrocyte
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
TAMDI	Theoretical Added Maximum Daily Intake
WHO	World Health Organization