Quinine-containing beverages may cause health problems

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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.

1 Subject matter of the assessment

BfR was asked to undertake the health assessment of quinine-containing beverages. The major objective was to clarify whether there is any scientific evidence of a possible association between the consumption of quinine-containing beverages and the isolated occurrence of health disorders in pregnant women and their newborn babies. The more recent reasons consist in the possible link between the consumption of quinine-containing beverages during pregnancy and the occurrence of health disorders in the mother and child. Furthermore, it was to be clarified whether, in addition to the prescribed labelling, a warning
for specific groups of persons (e.g. pregnant women) should also be prescribed for quinine-containing beverages. Against this backdrop reference is made to the second recital in Directive 2002/67/EC on the labelling of foodstuffs containing quinine and of foodstuffs containing caffeine: “According to the conclusions of the Scientific Committee on Food, there is no objection from the point of view of toxicology to the continued use of quinine at a certain maximum level in bitter drinks. However, consumption of quinine may be counter-indicated for certain people for medical reasons or because they are hypersensitive to the substance.”

2 Results

Although in the current case BfR was unable to identify any association after careful examination, the Institute recommends – on the basis of the currently available data and in line with the existing contraindication for quinine-containing medicinal products – to abstain from quinine-containing beverages during pregnancy. Along the lines of preventive health protection this recommendation reflects the numerous gaps in knowledge and the low safety margins between exposure doses and NOAEL (no observed adverse effect level) or between toxic doses and pharmacological effective doses. Furthermore, this recommendation upholds the principle that health protection in the food sector should at least be on a par with risk reduction measures in the medicinal product sector whereby pregnant women, unborn babies and infants are to be deemed to be groups requiring special protection.

Besides pregnant women, other groups of individuals for which there is a contraindication in the medicinal product sector (for taking quinine to treat nocturnal calf muscle cramps or for taking cinchona bark and its preparations) should also refrain from drinking quinine-containing soft beverages. These are people who suffer from tinnitus or pre-existing damage to the optic nerve, glucose-6-phosphate-dehydrogenase deficiency (symptoms: haemolytic anaemia), myasthenia gravis or hypersensitivity to quinine or cinchona alkaloids. Individuals suffering from cardiac arrhythmia or who are taking medicines that interact with quinine, should only consume quinine-containing soft drinks after consulting their doctor. This applies in particular to anticoagulant medication as there have been reports of cases in which the dose of anticoagulant preparations had to be reduced following higher consumption of tonic water. For motor vehicle drivers, the mention of possible visual disturbances after consuming larger amounts of bitter beverages is relevant.

BfR believes that measures are needed to adequately inform the risk groups concerned. Furthermore, BfR recommends explaining the symptoms of cinchonism and quinine hypersensitivity to consumers and advising them to stop their quinine intake immediately and to immediately consult a doctor when these symptoms occur. BfR recommends that the 1988 assessment of the Scientific Committee on Food should be updated and in this context efforts should be made to establish a coordinated consumer information within the EU.

3 Reasons

3.1 Risk assessment

3.1.1 Agent

Besides its isomer quinidine, quinine (6-methoxycinchonan-9-ol, CAS No. 130-95-0) is the most important principal alkaloid of cinchona bark (Cinchonae cortex), the dried bark of Cinchona pubescens, Vahl (synonyms: Cinchona succirubra, Pavon; family: Rubiaceae). The salts of quinine are mainly used in medicinal products. Furthermore, because of its
characteristic bitter flavour, it is used in foods, particularly in soft drinks (e.g. tonics, bitter lemon drinks).

3.1.1.1 Food law provisions

According to Directive 2002/67/EC of the Commission of 18 July 2002 on the labelling of foodstuffs containing quinine, and of foodstuffs containing caffeine and/or the corresponding provisions of the Food Labelling Ordinance of 15 December 1999 (last amended on 16 January 2004) quinine and its salts, which are used as flavourings in the production or preparation of a foodstuff, must be mentioned by name in the list of ingredients immediately after the term “Flavouring”.

The Council Directive of 22 June 1988 (88/388/EEC) on flavourings for use in foods does not set any maximum levels for quinine or its salts. In consequence there are separate national provisions. The latest version of the German Flavourings Ordinance of 22 December 1981 (Annexes 4 and 5) gives for quinine, quinine hydrochloride and quinine sulphate the following maximum levels in ready-to-eat foods, calculated as quinine: total 300 mg/kg in spirits and 85 mg/kg in non-alcoholic beverages. Other beverages or foods may not contain quinine as a flavouring pursuant to Annex 4 to the Flavourings Ordinance. Furthermore, §5 of the Flavourings Ordinance stipulates the inclusion of the wording “contains quinine” in the labelling of flavourings which contain quinine or its salts.

3.1.2 Hazard potential and exposure

Most knowledge about the action profile of quinine derives from its pharmaceutical use. Hence, an overview is first given of the spectrum of pharmacologically and toxicologically relevant effects and related aspects described in the relevant literature; attention also focuses on dose relations. Section 3.1.2.2 deals with the opinions of international bodies on the risk assessment of quinine use in foods. This assessment is based on literature searches on the current topic in the DIMDI database xtoxlitall.

3.1.2.1 Quinine in medicine

3.1.2.1.1 Current uses

Malaria treatment
Quinine has been used as a pure substance since 1820 to treat malaria and fever attacks. The development of synthetic malaria medicines led to the almost complete abandonment of this application. However, since the middle of the previous century it has been once again growing in importance as a consequence of the appearance of chloroquine-resistant strains of *Plasmodium falciparum* (1, 2). The malaria treatment lasts between 1½ - 2 weeks with oral administration of quinine salts at doses which correspond to at least 0.8 – 1g free quinine base (molecular weight: 324.4) per day (e.g. daily dose of 1 – 1.25 g quinine hydrochloride dihydrate) (molecular weight: 396.9) or 1.95 g quinine sulphate dihydrate (molecular weight: 783) (1-6).

Peripheral muscle relaxant
Single oral doses of 200 mg quinine sulphate dihydrate a day, equivalent to 166 mg free quinine base, are applied in the treatment for nocturnal leg cramps. If necessary, the dose can be doubled (2, 3).
In the USA the Food and Drug Administration (FDA) advised against the use of quinine sulphate products to treat nocturnal calf muscle cramps because of the unfavourable risk-benefit ratio particularly for older patients (9).

A meta-analysis of the efficacy of quinine or quinine salts to treat nocturnal leg cramps in older people revealed that quinine sulphate reduced the number of muscular cramps compared with the placebo. According to the authors, the study results point to accumulation in conjunction with repeated doses which means that treatment lasting at least four weeks may be necessary in order to achieve the desired effect (35).

There is no known threshold dose upwards of which the muscle relaxing effect occurs.

3.1.2.1.2 Pharmacodynamics

Quinine destroys erythrocytic schizonts (dividing stage of the protozoan in red blood cells) in all forms of malaria in humans. Discussions focus on whether the mechanism is based on intercalation. The quinine molecule intercalates itself between the bases of the parasite DNA and inhibits nucleic acid synthesis (5, 6). Vis a vis other unicellular organisms (e.g. bacteria, yeast) and spermatozoa, quinine also manifests a more or less destructive effect (6). Some of the areas of use outlined above refer to the analgesic (pain-relieving), antipyretic (fever-reducing), local anaesthetic and muscle-relaxing effects of quinine. The muscle-relaxing effect is based on the antagonistic action to physostigmine on the skeletal muscles as also exhibited by curare. The excitability of the motor end plate is reduced by quinine and reactions to repeated nervous stimuli and acetylcholine are reduced by quinine (2, 5, 6). On the gravid uterus quinine has a slightly oxytocic effect. In the past quinine was, therefore, used in the induction phase of birth at an oral dose of between 300 and 500 mg twice daily in order to induce labour although this effect has not been verified (7). It is no longer administered for this purpose. There are numerous case reports of the ingestion of high doses of quinine (mostly several grams) to self-induce abortion (cf. 3.1.2.1.6).

3.1.2.1.3 Pharmacokinetics

After oral administration quinine is almost completely absorbed. Maximum blood levels are achieved after 1 to 3 hours. Values of between 70-90% and of 4 to 12 hours for plasma half-life are given for plasma protein binding. In the erythrocytes of healthy individuals, the quinine level is 3 to 5 times and in parasitised erythrocytes 20 up to 100 times higher than in plasma. In the other organs distribution is largely even. In the cerebral spinal fluid (CSF), however, only 7% of the serum values are reached at the same time. Quinine crosses the placenta barrier and quickly reaches foetal tissue. On the basis of older studies it was presumed that maternal reabsorption of quinine from the foetus is slow and excretion in foetal urine is limited so that quinine may accumulate in foetal tissue (36, 37). Quinine can be detected in human milk. It is subject to high metabolism in the liver and 95% is excreted as metabolites and 5% in unchanged form in urine. There are some reports that even after treatment spanning several days, there was no accumulation (2, 6). In the case of an acidic urine pH, excretion is accelerated, and slowed down in the case of an alkaline pH. The latter can also lead to elevated quinine plasma concentrations and may reinforce possible toxic effects (1, 2, 5, 6, 9).
3.1.2.1.4 Adverse reactions

Concerning the use of quinine-containing medicines to treat malaria or nocturnal leg cramps, adverse effects are mentioned which occur relatively frequently in the therapeutic dose range in conjunction with long term or repeated administration (manifestations: CNS, gastrointestinal tract, skin). They are classed together as cinchonism. The current Rote Liste ® mentions the following adverse reactions (3):

- Neurotoxic effects (e.g. headache, tinnitus, visual disturbances, confusion)
- Gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea)
- Exanthema (cf. h)
- Cardiac stimulus conduction disorders
- Fall in blood pressure (at high doses)
- Kidney damage (rare)
- Haematological disorders (cf. h) (e.g. haemolytic anaemia, leucopenia, thrombopenia, hypoprothrombinaemia)
- Hypersensitivity reactions (e.g. skin reactions, drug fever, bronchospasms, changes in blood count, liver disorders, isolated cases of disseminated intravasal coagulation).

International publications point out that cinchonism involving auditory and visual disturbances may already occur after low quinine doses (9) in individuals who are hypersensitive to quinine and that ototoxic and oculotoxic symptoms are included amongst the set of symptoms of quinine hypersensitivity (2). Of the hypersensitivity-related changes in blood count, medical literature focuses – apart from the thrombocytopenic purpura (see 3.1.2.3.2) caused by small quinine intakes from bitter beverages – on blackwater fever. It has been observed as a rare hypersensitivity reaction to quinine intake during pregnancy and malaria treatment (2, 6, 9) (cf. also 3.1.2.1.6). The trio of massive haemolysis, haemoglobinaemia and haemoglobinuria are described as “blackwater fever”. It can lead to anuria, kidney failure and even death. It is presumed that in these cases as well as in milder forms of quinine-related haemolysis, the main individuals affected are those with a genetic glucose-6-phosphate-dehydrogenase deficiency (1, 2, 6, 9). Given the importance of this problem for the food sector, the former Federal Institute for Consumer Health Protection and Veterinary Medicine, BgVV, had already recommended in 2000 that SCF should examine the possibility of warnings.

Finally, one adverse quinine reaction which is not mentioned in the Rote Liste ®, that occurs both during the treatment of malaria and leg cramps, is the induction of hyperinsulinaemia and hypoglycaemia by stimulating beta cells of the Islets of Langerhans described in the literature. This can cause serious complications particularly during pregnancy (2, 9, 11).

3.1.2.1.5 Contraindications and precautions

The Rote Liste ® indicates pregnancy as a contraindication for the quinine doses used to treat both malaria and nocturnal leg cramps. The reasons given are oxytocic action and embryotoxicity at high doses (eye defects and deafness). The contraindications mentioned are tinnitus, prior damage to the optic nerve, glucose-6-phosphate-dehydrogenase deficiency (symptoms: haemolytic anaemia) and myasthenia gravis. In patients suffering from cardiac arrhythmia a precautionous dosage is recommended (3).

The pharmacological standard literature also mentions quinine hypersensitivity (1, 5, 6, 9), kidney and liver damage (1) as well as lactation (6) as contraindications (2, 5, 6, 9).
In the case of pregnant women suffering from life-threatening malaria, a risk-benefit analysis may conclude that treatment with quinine may be necessary under certain circumstances (9). The American Academy of Paediatrics (9) is of the opinion that quinine treatment can probably be tolerated during lactation.

3.1.2.1.6 Administration of therapeutic doses of quinine during pregnancy, misuse of quinine as an abortifacient

Publications on the adverse, toxic effects of quinine on the maternal organism or the foetus mostly refer to quinine intakes as an abortifacient and less frequently to therapeutic applications.

In the older literature there are reports on the pharmaceutic application of quinine to promote contractions during the induction phase of birth (cf. 3.1.2.1.2) and for the purpose of abortion in the case of foetal death in uteri whereby the oxytocic effect of quinine is described as uncertain (7, 8). Older studies on the use of quinine for the induction of labour showed that, besides the already mentioned possible quinine accumulation in foetal tissue, quinine treatment probably as a consequence of intrauterine respiratory depression (asphyxia) frequently led to meconium being excreted into the amniotic fluid (36, 37). More rarely an inadequate involution of the uterus was registered (37). The conclusions by King (37) that the induction of labour with quinine sulphate (repeated administration of 0.65 g, corresponding to 0.54 g quinine base) had led to the death of the foetus in several cases, was contradicted by the data in the two other studies (36, 38).

Concerning the treatment of severe forms of malaria during pregnancy, current literature points out that there are no indications that quinine may have an oxytocin-like effect in the third trimester of pregnancy (9). However this somewhat contradicts the findings by Looareesuwan et al. (11). The latter had examined the side-effects of quinine treatment in the last trimester of pregnancy in 12 patients suffering from severe falciparum malaria. The patients were given an initial dose of 10 or 20 mg quinine hydrochloride (equivalent to 8.3 and 16.7 mg quinine base) per kg bodyweight intravenously over a period of 4 hours, followed by 10 mg quinine dihydrochloride/kg bodyweight intravenously every 8 hours. Once they were able to swallow, treatment was continued with quinine sulphate tablets (no indication of dose) so that the total administration duration was 7 days. Uterus activity increased in the course of treatment in two cases, whereby in one patient the frequency increased and in the other, the amplitude of the uterus contractions. The labour pains had not started in either of the two women; in both cases malaria must also be considered as the factor that triggered contractions apart from quinine. Out of the three patients who were in labour, two gave birth normally whereas the third had a Caesarean section because of intrauterine hypoxia of the foetus. 7 out of 12 patients developed hypoglycaemia and hyperinsulinaemia; in only two of the above mentioned cases did the patients already suffer from these conditions prior to the administration of quinine. The authors come to the conclusion that in the last trimester of pregnancy, it is not the oxytocin-like effect of quinine but rather its ability to induce the release of insulin which is to be regarded as its most important toxic effect (cf. also 3.1.2.1.4).

In older articles various cases were compiled in which maternal as well as foetal toxicity effects were described following the abusive ingestion of quinine as an abortifacient. However, frequently no further information is available like e.g. on the use of other abortion agents (8, 12-14). Dannenberg et al. (8) identified e.g. 70 cases in which quinine was administered to terminate a known or suspected pregnancy. At least 11 of them (16%) led to death of the mother, in at least 41 cases (59%) the offspring manifested congenital
anomalies for which quinine was thought to be the cause. Only in 3 cases (4%) did abortion take place without maternal death. Acute kidney failure and acute haemolytic anaemia were the main causes of the maternal fatalities (cf. 3.1.2.1.4). In the other cases mainly reversible kidney failure, cinchonism, lengthy auditory deficits and blindness were diagnosed in the patients (8).

In the context of various case descriptions of quinine-related intravascular haemolysis, followed by tubular necrosis and acute kidney failure during pregnancy there are repeated comments that haemolytic anaemias following quinine administration were most frequently observed during early pregnancy and that there was a wide variation in the individually tolerated dose. For instance in one case a pregnant woman died after taking only 0.4 g quinine (split into two doses) (15, 39-42). Discussions focus on whether the elevated sensitivity of red blood cells to quinine-related haemolysis in early pregnancy can be attributed to the fact that factors which normally inhibit haemolysis may be reduced during pregnancy (42).

Dannenberg et al. mentioned blindness, deafness and a wide range of physical anomalies as teratogenic effects with a suspected association to quinine administration. However no typical quinine malformation syndrome can be identified (8). Nishimura et al. (13) also refer to some of the cases analysed in (8). They sum up that after the oral ingestion of various quinine doses (from 1 tablet up to 30 g, normally 1-4 g total) during the first trimester of pregnancy (one exception) 21 cases of anomalies were described in 12 publications between 1949 and 1967. In 10 cases they affected the CNS (including 6 cases of hydrocephalus), 8 times the extremities (including 3 cases of dysmelia), 7 cases the face, 6 cases the heart, 5 cases digestive organs, 3 cases the urogenital tract (e.g. one newborn baby who died after 20 hours and whose mother had ingested 2.3 g quinine in the 6th week of pregnancy had no kidneys (8, 43)), 3 cases hernias with various localisations and one case vertebrae. In addition, Nishimura et al. quote two publications which reported on mentally retarded offspring in conjunction with quinine ingestion during pregnancy. Nishimura et al. comment that no clear conclusions on the teratogenicity of quinine as a medicament can be drawn as no systematic or epidemiological studies were available on human malformations induced through the therapeutical use of quinine.

3.1.2.1.7 Interactions

Quinine reinforces the effect of digoxin, digitoxin and muscle relaxants. In interaction with other cinchona alkaloids there may be a mutual amplification of effect. Quinine can suppress the biosynthesis of vitamin K dependent coagulation factors whereby the effect of anticoagulants can be increased. Quinine ingestion can also lead to elevated plasma levels of warfarin and related anticoagulants (2, 33) (cf. 3.1.2.3.2). As already mentioned, urine-alkalising agents can delay quinine excretion thereby amplifying the toxic effect (1-3, 5, 6).

3.1.2.1.8 Intoxications

The fatal oral quinine dose for adults with a healthy heart is 5 to 10 g and 1 to 2 g (5) for children who are deemed to be hypersensitive to quinine. The ingestion of 2 g quinine is life-threatening for adults with a heart complaint. Overdoses lead, among others, to severe central nervous disorders and cardiac complications. Death is caused by cardiac arrest or respiratory paralysis (3, 6).

3.1.2.2 Cinchona bark in medicine
The monograph “Cinchona cortex (cinchona bark)” of Committee E of the former Federal Health Office (16) lists for a daily dose\(^1\) of 1 to 3 g drug the indications loss of appetite and dyspeptic disorders (referring to the effect of promoting gastric juice and saliva secretion), the contraindications pregnancy and hypersensitivity to cinchona alkaloids and the interactions amplification of the effect of anticoagulants. It indicates as adverse reactions sporadic hypersensitivity reactions and, on rare occasions, an elevated bleeding tendency as a consequence of thrombocytopenia. In these cases a doctor should be consulted immediately. Furthermore, it is pointed out that ingestion may lead to sensitisation to quinine and quinidine.

Already in the commentary on the 9\(^{th}\) edition of the German Pharmacopoeia (10) the use of the composed cinchona tincture *Cinchonae tinctura composita* is described as “no longer to be recommended” because of the risk of allergenicity.

3.1.2.3 Quinine in foods

3.1.2.3.1 Expert opinions of international bodies

As far as the safe use of quinine in foods and, more particularly, in soft drinks is concerned, assessments are available from the Scientific Committee on Food (SCF) (17) from 1988 and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) from 1990 (18) and 1993 (19). They rely, amongst other things, on *in vitro* studies, animal experiments and human findings. Reference can only be made here to some excerpts and by way of summary of these data. For more detailed information please refer to the expert opinions mentioned in the references (17-19). In this context it should be pointed out that quinine or quinidine salts are classified in the EU Register of Flavouring Substances (20, 21) as substances for priority assessment (22).

In its assessment SCF comes to the following conclusions (17):

*The Committee is now assured that no adverse reproductive or teratological effects will result from the use of quinine in bitter soft 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/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 effect. This should 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.*

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\(^1\) Based on a quinine level of 0.8-4\% (5), a daily dose of 1 to 3 g cinchona bark in a drug corresponds to a daily dose of between 8 mg and 120 mg quinine, combined with other cinchona alkaloids.
The Committee sees no objection 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 summary assessment by JECFA from 1990 states (18):

COMMENTS

Biochemical studies, short-term studies in rats, teratology studies in rats, and mutagenicity studies were reviewed. In these studies, no-effect levels ranged from 40 mg per kg bw per day to 100 mg per kg bw per day. Mutagenicity studies were negative. Varied complaints including headaches and transient visual problems were reported in human volunteer studies using doses of 100 mg of quinine hydrochloride per person per day. These findings were not confirmed in a second, controlled study using 120 mg per person per day. A third study showed electronystagmographic changes in stressed subjects for which a no effect level of 52.5 mg quinine per person per day was determined.

The Committee concluded that a Temporary ADI could be established on the basis of the human data. In view of the fact that the toxicity of concern was acute and reversible in nature and that there is extensive experience of human consumption without reports of acute toxicity except very rarely in individuals with hypersensitivity, the Committee saw no need to require a margin of safety.

EVALUATION

Level causing no toxicological effect
Rats: 40 mg quinine hydrochloride/kg bw/day
Humans: 0.9 quinine mg/kg bw/day.

Estimate of temporary acceptable daily intake
0-0.9 mg quinine/kg bw/day.

This was updated by the JECFA Opinion from 1993 (19) with the following wording:

COMMENTS

The Committee concluded that the data demonstrated a clear NOEL with respect to the ocular effects of 80 mg of anhydrous quinine hydrochloride per day, equivalent to 72 mg of quinine free base. No treatment-related effects on audition or clinical biochemical abnormalities were observed at doses up to 160 mg of anhydrous quinine hydrochloride per day.

EVALUATION

The previously established temporary ADI was withdrawn and, in the light of data on levels of use in beverages, the results of the consumption study and the additional data on humans, the Committee concluded that current use levels in soft drinks of up to 75 mg/l (as quinine base) were not of toxicological concern. However, the Committee noted that a small group of consumers shows an idiosyncratic hyper-reactivity to quinine, and recommended that the consumer should be informed by appropriate means of the presence of quinine in foods and
beverages in which it is used. The contribution of other uses of quinine in food and alcoholic beverages to daily intakes was considered to be negligible.

This evaluation was again subject to change in the following way (44):

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 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 showed 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.

The short-term, oral studies in rats mentioned in the JECFA Monograph published in 1990 have since been published (23). Mainly because of the results of two 13-week studies, on the basis of which 40 and 60 mg quinine hydrochloride/kg bw/day were derived as the no effect level (NEL), the examiners stated that at high doses (100 and 200 mg/kg bw/day) quinine hydrochloride has a low-grade hepatotoxicity and that the kidney can be identified as a possible target organ (elevated plasma urea level combined with slightly elevated values of inorganic phosphorus, slightly elevated kidney weights in males, dose-related clearly higher water consumption of pregnant mice at 100 and 200 mg/kg bw/day (see following description of the rat teratogenicity study).

According to JECFA no long-term or carcinogenicity studies are available (18).

In the SCF and JECFA assessments it was also considered which studies were available that permitted statements about possible reprotoxic and embryotoxic effects. The JECFA (18) assessment points out that reproduction studies are lacking.

From the available animal teratology studies, JECFA (18) mentions a gavage study (23) (published in the meantime) in which four groups of 25 pregnant rats were administered oral doses of 0, 50, 100 or 200 mg quinine hydrochloride per kg bw/day from day 6 to day 15 of pregnancy. In accordance with the findings of the 13-week feed studies, the dams in the two upper dose groups showed lower body weight gains than the control animals. The clearly higher dose-related water consumption of the dams in the groups with 100 and 200 mg/kg bw/day is noticeable. The investigators discussed this in conjunction with the influenced parameters of the 13-week studies which affected kidney function (see above). However, in the case of the animals investigated there, no elevated drinking water consumption was observed. Litter and foetal weights (means) were significantly reduced in the highest dose group. There was a significant increase in the total of variants of the sternebrae (ossification centres in the sternum segments) and a slight increase in the 100 mg/kg bw/day dose group compared to controls. There are no differences in pregnancy data, total of resorptions, litter size, sex ratio or major malformations between dose groups. The number of visceral anomalies appeared to be elevated in the highest dose group compared with the other groups (not significantly). The authors concluded that the 100 mg/kg bw/day group showed no adverse effects on embryo or foetal development.

In another rat study (24) published by Lapointe and Nosal two groups each consisting of 5 dams were given either 0 or 0.25 mg/ml quinine in their drinking water, starting two weeks prior to gestation and continuing throughout gestation and lactation (approximately 40 mg/kg
bw/day). Pups from the quinine treated dams weighed significantly less at birth, had significantly delayed eye opening and teeth eruption, and one neonate each was observed with syndactylyia in the right forelimb or anophthalmia of the right eye. Given the low numbers in the groups and other shortcomings, the results must be viewed as not completely reliable (18).

Furthermore, unpublished teratogenicity studies on deoxyquinine, a degradation product of quinine which is formed through exposure to sunlight, were included by SCF and JECFA in the assessments (17, 18). In one study four groups each with 30 rats were dosed by oral gavage with either 0, 6.67; 20 or 60 mg/kg bw/day from day 6 to day 15 of gestation. 20 animals in each group were killed and the foetuses examined. The development of the offspring was examined regarding the remaining 10 animals. The mean litter sizes in the 6.67 and 60 mg/kg bw/day groups were reduced; this was attributed by the research scientists to pre-implantation losses not related to treatment. There were an increased percentage of foetuses with 14 ribs in the 60 mg/kg bw/day group. The investigators did not observe any treatment-related developmental effects (assessment of incisor eruption, pinna unfolding, eye opening, startle response, pupil reflex, surface righting reflex, air righting reflex). The authors concluded that there were no significant adverse treatment-related effects at the levels of deoxyquinine used in the study (17, 18).

In another oral study (oral gavage) 4 groups of 15 rabbits were dosed by gavage with either 0, 20, 40 or 80 mg/kg bw/day of deoxyquinine from day 6 to day 18 of gestation. In the high dose group 3 animals died shortly after treatment; the other animals showed reduced weight gain from day 10 to day 23 of gestation. The investigators did not observe any significant treatment-related developmental toxicity. In a prior orientational study weight loss, increased mortality, anorexia, behavioural changes, cramps and collapse were observed in parent animals at a dose of 135 mg/kg bw/day (17, 19).

In the SCF assessment other teratogenicity studies on quinine are given as references without any further details (17). For instance the studies by Tanimura (12) revealed that after oral administration of doses of quinine hydrochloride of 20, 100 or 200 mg/kg bw/day to a total of 6 apes (macaca fuscata or macaca mulatta) from day 27 to day 29 of gestation, the only anomaly observed was a 13th rib in one foetus (20 mg/kg bw/day). Retroplacental haematomas and / or yellowish amniotic fluid in 2 out of the 6 treated animals (20 and 100 mg/kg bw/day) were taken as possible signs of abortive effects. The publication by Tanimura lists the results of ten older teratogenicity studies in various species with differences concerning dose, treatment interval and mode of administration. The results of two studies do not point to any embryotoxicity or malformations whereas in the other ones degeneration of the auditory nerve and ganglion cochlear, mitochondrial changes and haemorrhagia in the cochlea as well as repeated CNS anomalies (like anencephaly and microcephaly), retarded growth and death in the uterus were noted.

3.1.2.3.2 Case reports and individual opinions on quinine-containing foods

Some scientific publications consider the problem of adverse reactions or drug interactions as a consequence of the consumption of quinine-containing soft drinks (25-34). Publications thematising the occurrence of visual and auditory disorders as well as headache following the consumption of quinine-containing tonic drinks and the derivation of the corresponding no observed adverse effect level (25-27) were discussed in more detail in the SCF and JECFA reports (17-19). From other publications we know that severe hypersensitivity reactions can sometimes be triggered by the consumption of quinine-containing soft drinks (e.g. one glass bitter lemon). There are reports, for instance, of thrombocytopenic purpura indicated as
“bitter lemon purpura” or haemolytic anaemias, which in some cases were complicated by kidney failure; in this conjunction disseminated intravasal coagulations were diagnosed (28-31).

For the present question a publication by Evans et al. (32) is particularly relevant. The authors reported about a neonate, which was described as jittery 24 hours after birth. These symptoms were still diagnosed on days 7 and 15, but not 2 months after birth. From the 24th week of pregnancy until birth in the 41st week of pregnancy, the mother had drunk 1,136 ml tonic water daily. This is equivalent to a daily quinine intake of 60 mg. During this time she had suffered twice from tinnitus. On the 7th day after birth maternal blood was tested negative for quinine, however quinine could be detected in the infant’s urine. The authors believe that quinine withdrawal caused the infant’s symptoms. They explain that quinine increases the refractory period of skeletal muscles and that the withdrawal of quinine had probably led to disinhibition of the skeletal muscles.

Furthermore, cases have been published in which the quinine intake from larger amounts of tonic water led to the need to readjust anticoagulant treatment. For instance one patient’s condition had been kept stable for months by administering 6 mg warfarin/day when her daily warfarin requirements suddenly fell to 4 mg or below. The cause was determined to be the daily consumption of 1-1.5 l tonic water. Once she stopped drinking this, the warfarin dose had to be readjusted to its original level. In a second patient, it was suddenly necessary to reduce the daily warfarin dose from 4 mg to 2 mg whereby there were readjustment difficulties over a few days. Here, too, a high consumption of tonic water (more than 2 l daily) was determined to be the cause. Referring to a quinine level of 79 mg/l of the consumed soft beverages the author assumes a daily quinine intake of 80-180 mg by his patients (33).

Regarding the relevant publications on the consumption of quinine-containing soft drinks (23, 25, 26, 32, 33), Berglund (34) made the following comments in the journal “Toxicology”:

It is unfortunate if the public is given the impression that drinks containing quinine are safe. Transient blurring of vision can be disastrous if experienced by air plane pilots or motor vehicle drivers. Interaction with warfarin and neonatal withdrawal jitteriness should be of concern.

Finally, attention should be drawn to non-official information on the Internet in which the drinking of tonic water is recommended for pregnant women as a way of preventing or treating the onset of nocturnal leg cramps. Other websites, by contrast, advise against the consumption of tonic water during pregnancy because of its potential labour-inducing effects.

3.1.2.3.3 Exposure to quinine-containing soft drinks

According to SCF, which drew on information from UNESDA (Union of European Carbonated Beverages Associations in EU Countries), non-alcoholic tonic beverages have a maximum quinine content of 80 mg/l and bitter lemon drinks a maximum quinine content of 45 mg/l. Furthermore, some alcoholic aperitifs contain quinine (approximately 10 mg/l). However, the substance would not be used in other foods (17).

Whereas the SCF report (17) had to refer to consumption data from older market studies (cf. 3.1.2.3.1), JECFA (19) quotes data from a more recent consumption study of consumers of quinine-containing soft drinks in the United Kingdom, France and Spain (Quinine Consumption Study, unpublished report, Cadbury Beverages Inc., 1991). According to this average quinine intake over 14 days was between 6.1 and 9.3 mg/person/day.
(90th percentile); the maximum quinine intake on one individual day ranged from 75 mg/person in France to 104.4 mg/person in the United Kingdom (based on a body weight of 60 kg maximum exposure values of 1.25 mg/kg bw/day and 1.74 mg/kg bw/day, respectively, are calculated). With a content of 80 mg quinine/l this would correspond to consumption between 940 and 1,300 ml of the beverage per person per day. This intake seems to be realistic in individual cases as quinine-containing soft drinks may be the main source of fluid to quench thirst and they are sold in comparatively large bottles (e.g. with the volume of 1 litre). This is confirmed by the case descriptions outlined above (cf. 3.1.2.3.2).

Regarding the consumption of quinine-containing soft drinks by special risk groups, there are no known exposure data aside from one study from the United Kingdom mentioned in the SCF expert opinion (17). According to this study children up the age of 15 years account for 1% of the total consumption of tonic and approximately 5% of the total consumption of bitter lemon drinks.

As far as consumption during pregnancy is concerned, it can be assumed that women who drank quinine-containing soft drinks regularly and/or in larger amounts as thirst quenchers prior to pregnancy will continue to do this during pregnancy. Thus even pregnant women may have daily maximum exposures of around 100 mg/person/day. Also relevant for risk assessment is the possibility that women drink larger amounts of quinine-containing soft drinks during pregnancy than they did before by following unofficial advice e.g. to alleviate nocturnal leg cramps, overcome morning sickness or replace alcoholic beverages.

3.1.3 Assessment and discussion

3.1.3.1 Consumption during pregnancy

In its assessment BfR focuses on whether quinine intake from soft drinks during pregnancy could result in adverse reactions for the maternal organism and/or offspring. As quinine-containing soft drinks may also be consumed during pregnancy to quench thirst, BfR assumes daily maximum exposure of about 100 mg quinine/person/day as a possible worse case scenario. Particularly with a view to pregnant women and their offspring, BfR believes that a risk assessment based on average daily exposures calculated from intakes over a longer period, is not justified as acute dose-response relationships should be analysed, too. Considering embryotoxicity short term exposure during a sensitive time span is relevant. For quinine various reprotoxic effects have been described for humans and animals. Both regarding foetal as well as maternal parameters there are however major gaps in knowledge particularly about dose-response relationships and threshold doses. Hence, a definitive risk assessment is not possible on the basis of the data mentioned above.

As far as embryotoxic (teratogenic) effects in animals (cf. 3.1.2.3.1) are concerned, a no observed adverse effect level (NOAEL) of 100 mg quinine hydrochloride/kg bw/day (equivalent to 82 mg quinine base/kg bw/day) was derived from a study in rats (23). This NOAEL only has a margin of factor 47 to the highest maximum daily exposure mentioned by JECFA of 104.4 mg quinine/person/day (equivalent to 1.74 mg quinine/kg bw/day) from quinine-containing soft drinks (cf. 3.1.2.3.3). This comparison implicates uncertainties as, contrary to what is normally required, no other embryotoxicity study with quinine in non-rodents (aside from the rabbit study with deoxyquinine) confirms the findings from the above-mentioned animal experiment. Furthermore, a second perinatal study in rats which is only reliable to a limited degree because of the inadequate test regimen (24) points to a lower NOAEL. In humans various teratogenic effects were linked to the ingestion of quinine as an
Abortifacient normally in doses of total 1-4 g leading to a margin of around factor 10-40 to the above mentioned maximum daily quinine exposure from soft drinks (cf. 3.1.2.1.6).

What is of particular relevance for this risk assessment is a case of withdrawal symptoms and related major (albeit seeming reversible) health impairments in a newborn baby whose mother had regularly consumed amounts of tonic water during pregnancy that corresponded to 60 mg quinine per day (3.1.2.3.2). Because of the easy placenta accessibility, the intake of only 60 mg quinine per day already leads to foetal quinine blood levels which effect the foetal organism (i.e. probable elevation of the refractory time of the skeletal muscles) since there could not be any withdrawal symptoms if this was not the case. These facts also highlight deficits concerning present knowledge of quinine induced reprotoxicity. Aside from animal multi-generation studies, there are no reliable animal studies on perinatal or postnatal development either, in which exposure is not restricted (like in the above mentioned study by Colley et al. (23) or in the teratogenicity studies with deoxyquinine in rats and rabbits (cf. 3.1.2.3.1)) to the short phase of organogenesis but rather encompasses the entire process from foetal development over birth until the end of lactation, and which focus more particularly on prenatally induced functional abnormalities and behavioural changes in the post-natal course of development, too. There is no information on the threshold dose, possible sequelae or later developmental disorders concerning the effect of quinine on the foetus which led to the withdrawal symptoms. Beside this, there is also a need for research with respect to indications of quinine accumulation in foetal tissue which can be derived from old studies (cf. 3.1.2.1.3).

There are no sufficient data on dose-response relationships or threshold doses either concerning the oxytocic action of quinine which carries the risk of miscarriage or premature birth with all the associated risks. In the past doses of between 300 mg and 500 mg of quinine were administered twice daily (orally) to induce labour. However, this effect has not been confirmed (cf. 3.1.2.1.2). Because of the oxytocic effect of quinine, pregnancy is a contraindication for the treatment of nocturnal leg cramps with this agent(cf. 3.1.2.1.1 and 3.1.2.1.5). The dose used here corresponds to 166 mg free quinine base and is, therefore, only 1.6 times higher than the above-mentioned maximum daily intake of 104.4 mg quinine from bitter soft drinks. In the monograph of Committee E of the former Federal Health Office (16) pregnancy is also indicated as a contraindication for cinchona bark, the use of which as a medicine leads to quinine intakes which correspond to the quinine amounts consumed in bitter soft drinks (cf. 3.1.2.2). On the other hand, in conjunction with considerations whether severe cases of malaria should be treated with quinine during pregnancy, the oxytocin-like action of corresponding quinine doses in the third trimester of pregnancy is challenged (cf. 3.1.2.1.6). In this context other, unconfirmed indications of abortive effects in monkey trials at 20 and 100 mg/kg bw/day should be mentioned.

Another maternal effect of quinine, for which there is no known threshold dose, is the induction of hyperinsulinaemia and hypoglycaemia which were observed in the course of malaria treatment in the last third of pregnancy (cf. 3.1.2.1.6). Furthermore, it is known, particularly from the use of quinine as an abortifacient, that in early pregnancy quinine may trigger acute haemolytic anaemias as hypersensitivity reactions which frequently prove fatal. In one case this happened after ingesting only 0.4 g quinine (cf. 3.1.2.1.4 and 3.1.2.1.6). There are no known statistics about the scale and severity of hypersensitivity and other intolerance reactions during pregnancy following the consumption of quinine-containing soft drinks. These gaps in knowledge make risk assessment more difficult, too.

It has already been mentioned that, in the case of quinine from bitter soft drinks, amounts of an agent may be ingested that may have possible pharmacological effects and that are only
slightly lower than therapeutic doses (by a factor of 1.6). Otherwise this exceptional situation is only accepted in the food sector for certain central nervous stimulants (e.g. coffee) or depressants (alcoholic beverages). Not least the unofficial Internet recommendations to take tonic water for nocturnal leg cramps demonstrate the special position of quinine-containing bitter soft drinks. They show that the risk-prevention measures valid in the pharmaceutical sector are also relevant for the food sector. Here it should be taken into account that in the food sector there is neither medical advice or monitoring; nor are any comprehensive dosage instructions or risk information provided. Finally, attention is drawn to one unclear aspect of quinine accumulation: the findings of a meta-analysis of the efficacy of leg cramp treatment point to the accumulation of repeated quinine administrations. However, this contradicts other pharmacokinetic information (cf. 3.1.2.1.1 and 3.1.2.1.3).

Based on the data currently available and for the purposes of preventive health protection, BfR advises against consuming quinine-containing beverages during pregnancy. This recommendation is made on the basis of the existing contraindication during pregnancy for the administration of quinine-containing medicine for the treatment of nocturnal leg cramps and of cinchona bark containing pharmaceuticals. This recommendation not only reflects the numerous gaps in knowledge and low safety margins from exposure doses to NOAEL and toxic or pharmacological doses respectively, but also the report on the health disorders of a newborn baby sustained after regular daily tonic water consumption by its mother (intake of 60 mg quinine/day) during her pregnancy (cf. 3.1.2.3.2). Furthermore, this recommendation upholds the principle that health protection in the food sector should at least be on a par with risk reduction measures in the pharmaceutical sector whereby pregnant women, unborn babies and infants are to be deemed to be groups requiring special protection.

3.1.3.2 Consumption by other groups of people

Based on the general comments in Chapter 3.1.3.1.1 it is recommended that besides pregnant women, all those groups of individuals refrain from consuming quinine-containing soft drinks for whom the intake of quinine for the treatment of nocturnal leg cramps or of cinchona bark or its pharmaceutical preparations are contraindicated (3, 16). This applies to people who suffer from tinnitus, pre-existing damage to the optic nerve, glucose-6-phosphate-dehydrogenase deficiency (symptoms: haemolytic anaemia), myasthenia gravis or hypersensitivity to quinine or cinchona alkaloids (cf. 3.1.2.1.5, 3.1.2.2). People with cardiac arrhythmia (cf. 3.1.2.1.5) or who take medicine that interacts with quinine (cf. 3.1.2.1.7, 3.1.2.2), should only drink quinine-containing soft drinks after consulting their doctors. This applies in particular to anticoagulant treatment as there have been reports of cases in which the dose of the anticoagulant preparation had to be reduced after elevated consumption of tonic water (3.1.2.3.2). For motor vehicle drivers, the mention of possible visual disturbances after consuming larger amounts of quinine-containing bitter beverages is relevant (cf. 3.1.2.3.2).

Whether the recommendation to reduce the consumption of bitter soft drinks should also be made for breastfeeding women and children – according to the study from the United Kingdom quoted by SCF the latter account for 1 % of total consumption of tonic beverages and 5 % of total consumption of bitter lemon beverages – cannot be assessed on the basis of the knowledge currently available. There are no corresponding studies to answer this question, particularly about reproduction toxicology (3.1.2.3.1, 3.1.3.1.1). Furthermore, it has not yet been determined whether older people, too, are at higher risk as is mentioned in the literature in conjunction with the treatment of leg cramps (9) (3.1.2.1.1).
3.2 Management framework/measures

3.2.1 Special measures

The comments in Sections 3.1.3.1 and 3.1.3.2 indicate that the consumption of quinine-containing beverages for various groups of consumers is linked to a risk. For that reason BfR believes measures are needed to inform those concerned in an appropriate manner. Warnings on labels are, in principle, the preferred option. Given the amount of information to be communicated, it is not easy to convert this into practice. Risk groups requiring medical care for their disease could be given detailed additional information during their medical consultation and treatment.

Besides informing specific risk groups BfR also believes it is necessary to raise awareness amongst all consumers of quinine-containing soft drinks. They should be informed about the symptoms of cinchonism and quinine hypersensitivity (in particular neurotoxic effects like tinnitus, visual disorders, confusion; signs of thrombocytopenic purpura, for instance skin bleeding, haematomas). Furthermore, they should be advised to immediately stop ingesting quinine and consult a doctor if these symptoms occur.

BfR recommends updating the SCF assessment from 1988 and proposes a coordinated EU-wide approach for consumer information and future research.

Based on this opinion BfR will conduct a survey amongst the German Poison Information and Treatment Centres to ascertain whether there have been reports of intolerance reactions and interactions with medicinal treatment as a consequence of the consumption of quinine-containing soft drinks. Furthermore BfR will ask the Federal Institute for Drugs and Medical Devices (BfArM) for information on relevant reports of adverse reactions and the submission of previously unknown results.

3.2.2 General measures

The situation described above once again reveals that the lacking of a systematic recording of adverse reactions in the food sector considerably impedes the assessment of existing risks and, by extension, their eradication. It can be assumed that in many cases adverse reactions have not been notified whereby it is difficult to estimate the real number of unreported cases. For that reason BfR supports the setting up of a central body to record and systematically document adverse reactions observed in conjunction with the consumption of foods (cf. on this subject the Health Assessment of Energy Drinks (BgVV Expert Opinion, 18 March 2002: http://www.bfr.bund.de/cm/208/gesundheitliche_bewertung_von_energydrinks.pdf)).

The example of quinine-containing bitter drinks reveals that in certain cases (for specific foods and their components for certain risk groups) additional consumer information which extends beyond the information content of a label and is provided by an official source would be useful in order to minimise health risks. One option could be to give a contact address on the food label. Besides the telephone number and address, a website address could be presented where information prepared specifically for consumers could be obtained. This website could help consumers to orientate themselves in view of the diverse, often contradictory, information available on the Internet.

4 References


Cinchonae cortex (Chinarinde), Monographie, Bundesanzeiger Nr. 22a vom 1.2. 1990.

Bericht des Wissenschaftlichen Lebensmittelausschusses über Chinin, Stellungnahme vom 19. Februar 1988, Bericht EUR 11617 DE.

Toxicological evaluation of certain food additives and contaminants, WHO Food Additives Series: 26, 29-42, Quinine hydrochloride, World Health Organization, Genf.

Toxicological evaluation of certain food additives and contaminants, WHO Food Additives Series: 30, 81-85, Quinine, World Health Organization, Genf.


Toxicity studies with quinine hydrochloride, Toxicology, Vol. 54: 219-226.


Toxicity threshold of quinine hydrochloride following low-level repeated dosing in healthy


Quinine sensitivity: a new cause of the hemolytic uremic syndrome, Annals of Internal
Medicine, Vol. 119 (3): 243-244.

The ingestion by pregnant women of substances toxic to the foetus, The Practitioner,

33. Clark DJ, 1983.

Toxicity of quinine, Toxicology, Vol. 58: 237-238.

Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly

Further investigations into the death of the child following the induction of labour by

37. King EL, 1933.
Does quinine in the induction of labor have a deleterious effect on the fetus?

38. Marchetti AA, Fitch LE, 1943.
The effect of the antepartum administration of quinine on labor and the puerperium,

Fatal hemoglobinuria with uremia from quinine in early pregnancy, JAMA,
Vol. 106 (7): 529-532.

Acute hemolytic anemia from quinine used as an abortifacient, New England J. Med., 
Vol. 238: 120-121.

42. Lang PA, Jones CC, 1964. 
Acute renal failure precipitated by quinine sulfate in early pregnancy, JAMA, Vol. 188 (5): 
464-466.

43. Sylvester PE, Hughes DR, 1954. 
Congenital absence of both kidneys, BMJ, Vol. 1: 77-79.

Evaluation of certain food additives and contaminants, Forty-first report of the Joint 
FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series: 837, 
13, Quinine, World Health Organization, Genf.