Commission of the European Communities

food — science and technique

Reports of the Scientific Committee for Food

(Twenty-second series)

Report

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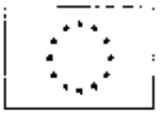

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A. Carere		(from 7 April 1988)
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Report of the Scientific Committee for Food on Antioxidants

(Opinion expressed 11 December 1987)

TERMS OF REFERENCE

To review the available data on the safety of antioxidants.

BACKGROUND

The Committee has carried out ad hoc reviews of the safety of a number of antioxidants over a period of time:

- gallates, 2 July 1976;
- tertiary butylhydroquinone (TBHQ) (unpublished);
- butylated hydroxyanisole (BHA), 29 April 1983;
- erythorbic acid (unpublished).

Following these evaluations, and particularly that of BHA, the Committee recommended that the safety of other antioxidants should also be assessed. This review became more pressing with the disclosure in 1983 of suspected adverse effects of butylated hydroxytoluene (BHT) in rats, and the Commission decided that the Committee should undertake a complete revision of a number of substances listed as antioxidants in the Directive on Antioxidants.

This view was undertaken up to March 1986 and the results made known to interested parties. In the meantime new data have become available, and prior to publication of the report the Committee (reconstituted in April 1986) has been asked to advise on whether these new data would affect the conclusions drawn in 1986.

The Committee believes that it would be premature to undertake a further major review at this time as clarification of a number of outstanding questions, particularly on BHA, is expected to become available during the next two to three years. At that time, or sooner, if the data are such as to warrant more immediate change, the Committee would wish to undertake a further comprehensive review of the safety of antioxidants. In the meantime the earlier conclusions remain valid.

The substances included in the review are :

L-ascorbic acid (E 300);
Sodium L-ascorbate (E 301);
Calcium L-ascorbate (E 302);
Ascorbyl palmitate (E 304);
Tocopherol extracts (E 306);
Alpha-tocopherol (E 307);
Gamma-tocopherol (E 308);
Delta-tocopherol (E 309);
Propyl gallate (E 310);
Octyl gallate (E 311);
Dodecyl gallate (E 312);
Butylated hydroxyanisole (E 320)
and Butylated hydroxytoluene (E 321).

Data were also provided on the antioxidants :

Tertiary butylhydroquinone (TBHQ)
and Erythorbic acid.

The Committee was assisted in its review by documentation provided by the Confederation of the Food and Drinks Industries of the EEC on the mode of action of antioxidants, the need for their use and possible hazards in the absence of antioxidants. Information on current national legislation reflecting current usage patterns was provided from the Commission files.

Committee members participated in an ad hoc working group of experts on antioxidants which took place 25, 26 October 1984.

Many toxicological data available only in summary form to the ad hoc working group were presented to the Committee during the present review. The main sources of toxicological data are referenced.

MECHANISMS OF OXIDATION

Unsaturated fatty acids are peroxidised in the presence of molecular oxygen by a three-step reaction involving free radical initiation, propagation and finally the appearance of secondary products (terminal process).

In the initiation step, the unsaturated lipid (LH) is converted via hydrogen abstraction into a lipid free radical L. in a process catalysed by light, heat or traces of transition metals. This carbon-centered radical is oxidised by molecular oxygen to a lipid peroxyl radical LOO. which is capable of participating in the initiation process by abstracting

hydrogen from another lipid molecule (LH) thus leading to propagation of the oxidation reaction. The lipid hydroperoxide formed by hydrogen donation to the peroxyl radical decomposes by secondary reactions to a wide variety of monomeric and polymeric products the chemistry of which is not yet fully understood. In the terminal process, low molecular LO. which in turn will break down on heating or metal catalysis to various types of secondary products including aldehydes, ketones, alcohols, esters, alkyl radicals and short chain hydrocarbons.

$LH \longrightarrow L. + H.$

$L. + O_2 \longrightarrow LOO.$

$LOO. + LH \longrightarrow LOOH + L.$

$LOOH \longrightarrow LO. + OH.$

Chain termination processes include :

$L. + L. \longrightarrow$ secondary products

$LOO. + L. \longrightarrow$ secondary products

$LOO. + LOO. \longrightarrow$ secondary products

the third of which is probably the most important at normal oxygen pressures.

Three essential objections to the presence of products of lipid peroxidation in food can be advanced :

1. A number of volatile secondary products give rise to off-odours and off-flavours which are not acceptable to the consumer.

2. The nutritional value of food may be decreased by the destruction of unsaturated fatty acids and of other essential food constituents possessing an unsaturated structure, e.g. Vitamin A.

3. Adverse health effects have been ascribed to the ingestion of lipid peroxidation products though this topic has not been extensively studied. It is, however, clear that :

(a) certain peroxidation products such as malonaldehyde and hydroperoxy derivatives of methyl linoleate and methyl linolenate are mutagens and that

(b) lipid peroxidation induced in vivo is associated with detrimental disturbances of membrane integrity and function. Rancidity itself may limit the intake of lipid peroxides.

ACTION OF ANTIOXIDANTS IN FATS AND OILS

Phenolic antioxidants (AH) interfere with lipid peroxidation by reaction with the radicals formed :

$LOO. + AH \longrightarrow LOOH + A.$

$LO. + AH \longrightarrow LOH + A.$

$L. + AH \longrightarrow LH + A.$

$OH. + AH \longrightarrow H_2O + A.$

Among these reactions, scavenging of the carbon-centered radical L. is assumed to be less efficient than scavenging of the oxygen-centered radicals, especially of the peroxyl radical LOO.. By removal of LOO. the antioxidant has a chain-breaking action; this action is most powerful during the early induction period when peroxide accumulation proceeds slowly but will be less successful once considerable peroxide levels have been achieved. At elevated temperatures when peroxide formation is accelerated optimal antioxidant concentrations are higher than those at room temperature.

Antioxidants are themselves converted into radical species during their inhibitory action on lipid peroxidation. These phenoxyl radicals A. undergo a variety of reactions :

1. The radical can be further oxidised to yield a stable quinone.

2. The parent antioxidant can be regenerated by reducing agents; this is a fundamental mechanism of synergism between individual antioxidants (see below).

3. Dimerisation can take place, and oligomers can also be formed.

4. The radical can form adducts with lipid peroxyl radicals to yield various non-radical species.

The fate of antioxidant-derived phenoxyl radicals has been studied in model systems using well-defined substrates such as a specific linoleic acid hydroperoxide or tert-butylhydroperoxide, and the structure of oligomers and adducts has been described. However, little is known about the fate of antioxidants in peroxidised fats and oils.

At very high antioxidant concentrations, the removal of the antioxidant-derived phenoxyl radicals by the processes listed above may be incomplete, and pro-oxidative effects of the remaining radicals may occur.

Optimum antioxidative concentrations at a given temperature do exist for phenolic antioxidants, notably tocopherols, which when exceeded result in decreased instead of increased stability of the fat or oil to be protected.

SYNERGISM

Synergism can take place between two antioxidants or between an antioxidant and another type of compound. Two fundamental mechanisms of synergism can be described :

1. The synergist acts by regenerating the parent antioxidant molecule AH from the phenoxyl radical A. which has been formed by the protection process. The synergism between ascorbic acid, ascorbate or ascorbyl palmitate on the one hand and tocopherols on the other hand is commonly ascribed to such action. The action of Vitamin C coumpounds on peroxidising lipid may however not be restricted to such synergist effects; a scavenger effect on peroxyl and alkoxyl radicals has not been excluded. The synergism between BHA and BHT has been studied in a model system using the peroxyl radical prepared from tert-butylhydroperoxide, and it was shown that the BHA phenoxyl radical accepts hydrogen from BHT to regenerate BHA while BHT itself is oxidised to the quinone methide.

2. Functional synergism is present between phenolic antioxidants and metal sequestering agents like citric acid, phosphoric acid or EDTA; the latter will decrease the concentration of free transition metal ions and thus remove highly active catalysts of the initiation process and of the hydroperoxide decomposition process.

The present Council Directive on antioxidants in food contains a list of substances which enhance the antioxidant effect of primary antioxidants. The safety in use of these substances which may also fulfil other technological functions in food is presently being reviewed by the Committee.

Citric acid and phosphoric acid are particularly useful in vegetable oils, but not animal fats. This has been ascribed to the fact that, while vegetable fats contain significant quantities of tocopherols, animal fats usually contain very little. Hence the acids involved in this synergism cannot fulfil their function.

NEED FOR ANTIOXIDANTS

Antioxidant technology is important in preserving edible fats, oils and lipid-containing food from development of objectionable flavours and odours, such as those resulting from oxidative rancidity and from formation of decomposition products which, as mentioned earlier, may be harmful. Furthermore, the nutritional quality of foodstuffs may be decreased by the oxidative loss of the fat soluble Vitamins A and E, or of unsaturated fatty acids. Antioxidants, to be effective, must be used with food materials of good quality. They will not protect (or mask) fat or fatty food which has already deteriorated from abusive storage or which was prepared from unsound raw materials. Best results can be expected only if the antioxidants are incorporated promptly into freshly-prepared products of good quality and if these products are subsequently packaged properly and stored under correct conditions.

The Committee was informed that antioxidants are used for a number of purposes. They can be of use in maintaining organoleptic quality by avoiding rancidity. There is economic benefit in the extension of the shelf-life of the foodstuff (this may be of significance for foodstuffs processed in one country and sold in other EEC countries or for foodstuffs of low consumption, for which a long shelf-life is desirable). As regards the technological benefits, very often the final processor of the foodstuff has to store an oil or fat used as an ingredient. These ingredients need protection during storage and before further processing can take place and the antioxidant has technological usefulness in maintaining the ingredient in good quality.

Information submitted to the Committee suggests the principal, but not exclusive, uses of antioxidants are to be found in the following groups of foodstuffs.

Vitamin preparations - preservation of vitamin content

Flavours) - sensitive compounds, e.g. terpenes, aldehydes oxidize essential
oils) easily

Animal fats)
Butter fat)
Vegetable oils)

Shortenings) - protection of the oil or fat component of the product

Biscuits)
Crisps)
Snack foods)
Nuts)

Chewing gum) – preservation of the unsaturated nature of the gum base; antioxidant remains in the base and is not normally ingested in significant quantities

Dried soups) – protection of unsaturated fatty acids which give the characteristic flavour

Mayonnaise and emulsified sauces) – protection of oil content during storage

Salted margarines) – animal fat based margarines require additional antioxidant

Potato granules, flakes and powder) – protection of unsaturated fatty acids; protection of the product during processing and storage

LEVEL OF USE; DAILY INTAKE

The Committee was provided with information on usage levels of antioxidants in food in the EEC Member States. This information showed considerable differences in usage patterns. It appears that these differences have been caused by a combination of several factors (e.g. special rules on the types of oil which might be used for specific purposes, availability of particular antioxidants, recipe traditions, distribution network). For similar reasons, only limited information was available to the Committee on interchangeability of antioxidants and the consequences that could ensue if the use of one or other substance were to be curtailed.

Nevertheless, the Committee was given estimates of possible total intake of antioxidants which varied from about 14 mg/person/day based on theoretical calculations to about 1 mg based on statistics on production and sale of antioxidants in the EEC.

Neither approach takes into account the losses of antioxidants during processing. This varies according to the foodstuff in question and the antioxidant concerned. In the case of phenolic antioxidants used in biscuits and snack foods (their main use), the figures for loss are said to be of the order of 35% and 50-90% respectively.

The daily intake (maximum) of BHA has been estimated to be 4 mg in the Netherlands. BHT and gallates were not detected in the foods examined.

The Committee emphasised the need for more extensive information on the daily intake of antioxidants, including knowledge of the intake of individual compounds.

NUTRITIONAL IMPLICATIONS RELATING TO POLYUNSATURATED FATS AND OILS

This review is not concerned with the problems of diet or with consideration of the possible advantages or disadvantages of polyunsaturated fats in comparison with other fats. However, it should be noted that in the absence of antioxidants, the dietary level of polyunsaturated fats may fall.

TOXICOLOGICAL EVALUATION

A summary of the evaluations is given in Annex 1.

The Committee's assessments of individual substances are contained in Annex 2. However, some general comments are pertinent.

Many reviews have appeared on the biological effects of lipid oxidation products and their relevance to cancer. Lipid oxidation products have been implicated in the disruption of biological membranes, the inactivation of enzymes and damage to proteins, the formation of age pigments in damaged cell membranes, oxidative damage to the lung by atmospheric pollutants, and in the causation of cancer. It is postulated that chemical carcinogenesis results from oxidation of chemical agents into reactive intermediates; and experimental studies in which antioxidants, such as BHA and BHT, have been shown to possess anti-carcinogenic properties have been interpreted as demonstrating beneficial effects of anti-oxidant activity in scavenging free radicals. However, this is probably of little relevance to the use of antioxidants as food additives where the intakes are small compared with those employed experimentally - and there is no evidence that such direct benefits to health (as might arise from prevention of *in vivo* auto-oxidation) results from the ingestion of food to which antioxidants have been added for important technological purposes. Nor is it clear the extent to which ingestion of foods which in the absence of added antioxidants could contain lipid oxidation products would alter the actual intake of such products or be likely to lead to adverse health effects. Rancidity itself may limit intake.

In assessing the safety 'in use' of individual antioxidants the Committee raised questions of wider toxicological principle. The results of recent carcinogenicity studies with BHA and BHT (together with data from subsequent research into specificity and mechanism of action of BHA) made it necessary to consider both the concept of a threshold for tumorigenesis (in the absence of evidence of genotoxicity) and whether effects in the rodent forestomach should be considered significant for prediction of effects on human health.

The Committee considered that if such tumour production is either irrelevant in the context of risk to the consumer, or capable of being dealt with in the same way as any other toxic effect with a demonstrable threshold, then the usual safety factor should be employed in using a NEL to establish an ADI. Furthermore, if the tumorigenic properties of BHA and BHT in rodents are not considered important as predictors of possible effects in humans then there should be no need to carry out strictly comparable types of

long-term/carcinogenicity studies with other phenolic antioxidants. Likewise, if the effects of BHA on the rodent forestomach are not considered relevant for man, then distinction between other antioxidants on the basis of their ability to produce hyperplasia in this organ should not be part of the assessment of their safety in use.

The Committee recognised that there was a threshold for the non-genotoxic tumorigenic effects of BHA and BHT. In the case of BHT, it was decided that since the NEL for tumorigenesis is higher than that for haemorrhagic and other toxic effects, the ADI should be based on these latter effects, with a standard safety factor of 100. It was not considered necessary to ask for carcinogenicity studies of similar design to be carried out on other phenolic antioxidants. With BHA, although the Committee thought the effects on the rodent forestomach were unlikely to be relevant for man (and were reassured by results from species without a forestomach) they did not feel able to dismiss the forestomach findings completely - and used the NEL for induction of hyperplasia in the rat forestomach as the basis for setting an ADI, without using a greater safety factor than usual. Whether there is a need for further studies of induction of forestomach hyperplasia by other antioxidants, will depend on the results of ongoing studies with BHA.

The Committee recommended that the Commission carry out regular reviews of the toxicology and levels of use/intake of the food additive antioxidants. This is to ensure that the intakes of BHA and BHT are indeed acceptable, and that any changing patterns of use, in the wake of recent concerns with BHA and BHT, do not result in any undesirable increase in the use/intake of other antioxidants, given the possible need to use proportionately larger amounts of other compounds to achieve the same technological effects.

In the case of ascorbic acid and tocopherols, the Committee did not think it appropriate to set an ADI for a vitamin present naturally in the diet at far higher levels than would be contributed by their use as antioxidants.

ANNEXES

SUMMARY OF CONCLUSIONS

L-ascorbic acid	(E300)		
Sodium L-ascorbate	(E301)	Acceptable	
Calcium L-ascorbate	(E302)		
Ascorbyl palmitate	(E304)		
Isoascorbic acid (Erythorbic acid)		Not acceptable	
Tocopherol extracts	(E306)		
Alpha-tocopherol	(E307)	Acceptable	
Gamma-tocopherol	(E308)		
Delta-tocopherol	(E309)		
Propyl gallate	(E310)		
Octyl gallate	(E311)	Group ADI	0-0.5 mg/kg bw
Dodecyl gallate	(E312)		
Butylated hydroxyanisole	(E320)	Temporary ADI	0-0.5 mg/kg bw
Butylated hydroxytoluene	(E321)	ADI	0-0.05 mg/kg bw
Tertiary butylhydroquinone		Not acceptable	

ASSESSMENT OF INDIVIDUAL ANTIOXIDANTS

L-ascorbic acid, and its calcium and sodium salts

Ascorbic acid (Vitamin C) is present in many rapidly growing leafy vegetables, tomatoes, potatoes and fruits. Foods of animal origin are poor sources. Only L(+) ascorbic acid is used as a food additive.

Ascorbates are used as inhibitors of enzymatic browning, as antioxidants in a variety of foods and beverages.

Toxicological data from short-term, long-term, reproductive and teratogenicity studies were available and showed no evidence of adverse effects even at relatively high dosage (from 1-2 g/kg bw/d). Mutagenicity data show that ascorbic acid does not cause gene mutations and although in vitro tests suggest that it causes DNA strand breaks and chromosome damage, the limited in vivo data are negative. Ascorbic acid appears to be able to potentiate or inhibit the mutagenic effects of other chemicals.

Some studies in man indicated a diuretic effect at 5 mg/kg bw and glycosuria at 30-100 mg/kg bw - but these results were not confirmed in large scale, double blind studies. Daily therapeutic doses of the order of 100 mg/kg bw over a long period have not shown adverse effects.

It is estimated that the normal daily intake of ascorbic acid from natural sources is 30-100 mg. The Committee considered that the use of ascorbic acid and its calcium and sodium salts as food additives would represent only a very small fraction of the total dietary intake.

The Committee therefore decided it was inappropriate to establish an ADI for L-ascorbic acid and its calcium and sodium salts, which they found acceptable for food additive use.

Ascorbyl palmitate

Ascorbyl palmitate is presumed to yield ascorbic acid during digestion.

Ascorbyl palmitate is used as an antioxidant in cooking fats. The commercial material tested was thought to have contained 5–20% ascorbyl stearate and 80–95% palmitate. The data would therefore be suitable for evaluating the stearate.

Toxicological data from short-term (up to nine months) and long-term studies were available in which no adverse effects were noted at 0.25% in the diet. The formation of bladder stones in a few animals in high dose groups was not thought to be relevant for man.

The Committee decided that ascorbyl palmitate was acceptable, with ascorbic acid and its salts, for food additive use.

Isoascorbic acid – opinion expressed in September 1984

The Committee was asked to consider the safety in use in food of isoascorbic acid (erythorbic acid) as an antioxidant, particularly in meat products and in (imported) wines.

The Committee was informed that isoascorbic acid can be used in meat products for the same purposes as ascorbic acid, corresponding quantities having the same technological effect.

The use of isoascorbic acid in wine is not authorised at Community level but discussion has been taking place to amend these rules, at least as far as imports are concerned.

The Committee has not considered in detail the special problems that might exist for all salts of isoascorbic acid, but its opinion on the acid itself is valid also for the sodium, potassium and calcium salts.

Isoascorbic acid was evaluated by JECFA in 1961 and 1973. An ADI of 0–5 mg/kg bw was established by that Committee on the basis of a long-term study in rats. Since that time a considerable amount of additional studies have become available, which are concerned particularly with the biological behaviour of the substance. Therefore a reappraisal of the totality of the data had become necessary.

Although the apparent anti-scorbutic activity of single doses of isoascorbic acid is about 5% of that of ascorbic acid, large doses over prolonged periods will relieve the symptoms of scurvy. Isoascorbic acid is absorbed less efficiently and can compete with ascorbic acid for transport mechanisms. It reduces the ascorbic acid body pool and increases

ascorbic acid turnover, reduces its half-life and depresses the bioavaiability of ascorbic acid by almost 50%. Isoascorbic acid is largely excreted in the urine but the fate in the body of 30-50% is unknown; nor are the metabolites known. Some human tissues appear to have stereospecific uptake. Unpublished data suggest failure of isoascorbic acid to be transported into granulocytes and inhibition of ascorbic acid uptake in man. The available short-term and long-term studies are inadequate as only one dose level was tested. Although no adverse effects were noted, there is no information on reproductive function or teratogenicity. The biological competition with ascorbic acid may be of significance for people with marginal ascorbic acid intake. The estimated intake may be 6-8% of the daily ascorbic acid requirement.

The Committee concluded that the available data are inadequate for full toxicological evaluation of the substance. Furthermore, the Committee was aware of the possibility that the observed competitive interference of isoascorbic acid with the absorption and distribution of ascorbic acid, and the resultant depletion of body reserves of ascorbic acid, could be of significance for people with border line intakes of ascorbic acid. The Committee was therefore of the opinion that the use of isoascorbic acid in food and drink is not acceptable, and no ADI was established.

Tocopherol extracts; alpha-, beta-, gamma- and delta-tocopherol; alpha- tocopherol acetate

Vitamin E consists of a group of eight closely related compounds, namely four tocopherols and four tocotrienols. Particularly abundant in vegetable oils are alpha-, beta-, gamma- and delta-tocopherol. They all contain an hydroxy-bearing aromatic ring system and an isoprenoid side-chain, but differ in the number of methyl groups bound to the aromatic ring. There are three such methyl groups in alpha-tocopherol, two in beta- and gamma-tocopherol, and only one in delta-tocopherol.

Nutritional deficiency of Vitamin E in rodents leads to sterility and muscular weakness and atrophy. In humans evidence of tocopherol deficiency approaching the severity of that noted in animals has been observed in patients with long-standing fat malabsorption in association with clinical conditions such as neuropathy and myopathy. The specific molecular functions of the Vitamin E compounds is not known with certainty but there is good evidence that they are closely associated with lipids throughout the body and active in stabilizing highly unsaturated fatty acids in the cell against oxidation. A protective effect of tocopherols on the integrity of cell membranes is also established. In evaluating relative biological activities of the tocopherols including the anti-haemolytic and in vivo anti-oxidative activity, the number and position of the methyl groups in the benzene ring are important. The most active form is (d)-alpha-tocopherol. (d)-beta-tocopherol has about 25%-50% such activity; and (d)-gamma-tocopherol has about 10%-37% as much as (d)-alpha-tocopherol, depending on the assay used.

The recommended daily dietary intake of Vitamin E, expressed as (d)-alpha-tocopherol equivalents, is 10 mg/adult male and 8 mg/adult female. The recommended intake of Vitamin E increases during pregnancy and lactation by 1 and 3 mg/day, respectively. These intakes are likely to be met by the levls of tocopherols naturally occurring in many foods such as vegetable oils, cereals, nuts and leafy vegetables.

Clinical data are available indicating that adult humans can ingest for a few years daily doses of Vitamin E in the order of 100 mg or above without adverse effects. Hypervitaminosis has been reported in human beings only at oral dosage levels in excess of 400 mg/day. An increased mortality risk has been claimed to be associated with intakes of Vitamin E in excess of 1 g/person/day. On the whole, these data are not sufficient to assess long-term effects in human subjects of high intakes of Vitamin E.

In view of their antioxidant properties, tocopherols are also used as additives in food to prevent the destructive, non-enzymatic attack of molecular oxygen on the double bonds of the polyunsaturated fatty acids. The relative antioxidant efficiency of the different tocopherols in foods depends upon the nature of the substrate, the temperature and, possibly, the concentration. For example, gamma-tocopherol was more active than delta-tocopherol and much more than alpha-tocopherol in inhibiting oxidation of lard at 97°C, whereas gamma-tocopherol was the most effective, closely followed by the alpha-form, in protecting safflower oil at 63°C.

The tocopherols commercially available as food additives are mixtures of natural compounds (E306) or single synthetic (d,l) alpha-(E307), gamma-(E308) and delta-tocopherol (E309). The E306 obtained from vegetable oils is a mixture of (d) alpha-, beta-, gamma- and delta-tocopherol; the proportion of these four forms varies according to the source of the oil. Thus, for example, (d) alpha-tocopherol is predominant in sunflower and olive oil, whereas (d) gamma- and delta-tocopherols predominate in soybean oil. Other mixtures, called "mixed tocopherols" and "80-20 mixed tocopherols", are sold mainly for their Vitamin E activity, they contain not more than 5% or 20% of non-alpha-tocopherol respectively, the rest being (d)alpha-tocopherol. Under some circumstances, tocopherol esters (i.e. acetate and succinate) of (d) alpha- or (d,l) alpha-forms are also commercially available.

Metabolism and toxicity data are almost entirely based on studies of alpha-tocopherol and its acetate.

Ingested tocopherols are absorbed, translocated to tissues and metabolised (d) alpha-tocopherol is retained in the issues longer than other forms of Vitamin E.

Tocopherols (i.e. (d) alpha-tocopherol, (d,l) alpha-tocopherol and (d,l) alpha-tocopherol acetate) are characterised by very low acute oral toxicity. Several animal species can tolerate doses of 200 mg/kg bw without apparent toxic signs.

Conditions described as hypervitaminosis E, including changes in oestrus cycle and degenerative lesions of liver and myocardium, have been reported in guinea pigs, hamsters and rats on subchronic administration, particularly by intra-muscular dosage in the range of 1 g of alpha-tocopherol/kg bw or higher.

Chronic toxicity studies with (d,l) alpha-tocopherol acetate suggested a limit hepatic response to Vitamin E overload as judged by liver enzymes and weight. They also indicated the possibility of interactions with other vitamins, e.g. Vitamins A and K in the diet, and the need for preventing vitamin imbalance at high intakes of Vitamin E. However, a

dose-related onset of haemorrhage, controlled by Vitamin K supplementation, also occurs with BHT. Both antioxidants appear to act by altering the availability of Vitamin K. Apart from the fact that BHT is not a vitamin, the reasons for considering that its effect is "toxic", while that of tocopherol may reflect "vitamin imbalance" are based on differences in dose response and the fact that there is some evidence that tocopherol can also interact with Vitamin A. However, it should be pointed out that studies on the effect of low doses of tocopherol on the prothrombin time, in the absence of Vitamin K supplementation, have not been carried out. Studies in human subjects suggest that large doses of tocopherol only decrease the levels of Vitamin K dependent clotting factors in the presence of pre-existing abnormalities, e.g. warfarin therapy. At a dose level in rats of about 500 mg/kg bw/d and after Vitamin K supplementation, only some borderline and equivocal effects, such as vacuolation of hepatic macrophages, have been observed. Some metabolic effects (e.g. alterations in the levels of ADP, ATP, phospolipids and cholesterol in the liver, and in the excretion of thiamine and phosphorus) have been reported (abstracts only were available to the Committee) following subchronic administration of tocopherols and tocopherol esters to rats at dose levels close to or lower than 500 mg/kg bw. However, as indicated by the results of the long-term studies, these metabolic changes do not result in toxic manifestations on prolonged treatment.

No adequate reproductive or teratogenicity studies in mammals are available for tocopherols. Some investigations which only focussed on certain specific effects (e.g. fetal survival and resorption, and some testicular functions) have been carried out with (d,l) alpha-tocopherol acetate or (d) gamma-tocopherol, in several species, including rats, hamsters, rabbits and mice. These studies (which were only available as abstracts) did not indicate any adverse effects apart from increased mortality of off-spring in rabbits and hamsters at high doses (1 600 and 750 mg/kg bw respectively).

Several investigations have fed or injected rats or mice with various doses of (d) alpha-tocopherol, (d,l) delta-tocopherol or (d,l) alpha-tocopherol acetate and have reported no increased incidence of tumours. Some in vitro and in vivo experiments indicate that tocopherols may have a beneficial effect, interfering sometimes with the formation of mutagens or with the expression of carcinogenic effects.

Although only scanty information is available on the toxicity of beta-, gamma- and delta-tocopherol, the Commission, in view of the very large amount of experimental and clinical data available on alpha-tocopherol, and the chemical and biological similarity of the four tocopherols, decided to consider the four tocopherols and alpha-tocopherol acetate as toxicologically equivalent. The intake of tocopherols from natural sources will normally far exceed that from processed foods containing tocopherol as an antioxidant.

The Committee concluded that the use of tocopherols as antioxidants in food was acceptable and that it was not appropriate to establish an ADI.

Gallates - propyl-, octyl-, dodecyl-

These three antioxidants are the n-propyl-, octyl- and dodecyl-esters of 3,4,5-trihydroxybenzoic acid. The purity of the compound is not less than 99% for propyl gallate and not less than 98.5% for octyl- and dodecyl gallates. Gallates are used as antioxidants in fats and oils (alone or in combination with other antioxidants) to prevent rancidity and spoilage; the gallates have been shown to be more effective antioxidants than BHA and BHT. Other food additive uses of gallates include shortenings, baked goods, candy, dried-milk, chewing gum base and food packaging materials. Information on intake is only available for propylgallate and has been estimated to be from 0.03-0.2 mg/kg bw/d.

In 1976 the Scientific Committee for Food (2nd Series) established a group ADI for propyl-, octyl- and dodecyl gallate for 0-0.2 mg/kg bw. This ADI was the same as that allocated by the WHO/FAO Joint Expert Committee on Food Additives in 1976 and confirmed in 1980. It was based on a NEL observed in a reproduction study in rats of 1 000 mg of octyl gallate/kg feed, equivalent to 50 mg/kg bw, with the use of a 250-fold safety factor. Further data have since become available, including liver enzyme induction, mutagenicity, 2-generation reproduction, carcinogenicity (mouse and rat) and promotion/inhibition studies.

Metabolic data are scarce but it is clear that propyl gallate is absorbed well and hydrolysed to propyl alcohol and gallic acid. The latter is further metabolised. Octyl- and dodecyl gallates are however far less well absorbed and only a minor proportion is hydrolysed to the alcohol and gallic acid. The acute toxicity of octyl- and dodecyl gallate is less than that of propyl gallate, possibly explained by the difference in absorption/metabolism. Gallates are mainly excreted in the faeces.

Gallates may cause skin sensitisation and subsequent exacerbation of the resulting contact dermatitis occurs in some such sensitized individuals after ingestion of gallates.

Short-term toxicity studies in rats, mice, guinea pigs, dogs and pigs were available to the Committee. Also, at least six long-term toxicity/carcinogenicity studies in rats and mice have been carried out with propyl gallate. About half of these studies were old and/or inadequate. Nevertheless, there was no evidence of any increase in tumour formation. The NEL was 1 170 mg/kg feed in one study and 5 000 mg/kg feed in at least two other studies. With octyl- and dodecyl gallates only one long-term toxicity study was available. In this old study no toxicity, nor increase in tumour incidence was noted with 5 000 mg/kg feed. The Committee considered that 5 000 mg/kg feed, equivalent to 250 mg/kg bw could be considered the NEL. In short-term studies propyl gallate did not cause hyperplasia in the rat forestomach.

Propyl gallate was tested for inhibitory and potentiation effects on carcinogenesis. Propyl gallate showed clear inhibitory properties against the induction of tumours by DMBA and/or nitrosamines; and on the effect of hepatotoxic compounds.

Reproduction and teratogenicity studies were carried out with propyl- and octyl gallate. From these studies it was concluded that gallates are not teratogenic. On the contrary, gallates protected rabbits against the teratogenic potential of hydroxyurea. In the reproduction studies, 2 500 mg/kg feed produced a few minor effects but 1 000 mg/kg feed was without effect.

A range of mutagenicity studies (including dominant lethal), host mediated assay, in vivo cytogenetic, and Ames tests, with propyl gallate were negative. (No tests have been carried out for gene mutation in mammalian cells.) No data were available for octyl- and dodecyl gallate.

The Committee concluded that although a few data were available for octyl- and dodecyl gallates, the fact that these compounds appeared to be less toxic than propyl gallate made the use of a group ADI acceptable. The Committee confirmed the previously established NEL of 50 mg/kg bw but did not think that there was any need to continue to use a safety factor or 250. The usual factor of 100 was applied.

The Committee therefore established a group ADI of 0-0.5 mg/kg bw for propyl-,octyl- and dodecyl gallates.

Butylated hydroxyanisole (BHA)

BHA is predominantly (85% or more) 3-tert-butyl-4-hydroxyanisole (3-BHA) with 15% or less of 2-tert-butyl-4-hydroxyanisole (2-BHA).

The Committee had previously considered BHA in 1978 and 1983. At that time biochemical, short- and long-term toxicity/carcinogenicity data were available, together with results from mutagenicity, teratogenicity and reproduction studies. There was no multigeneration study. Some observations had also been made in man.

The SCF evaluated BHA in 1983 following consideration of results from a Japanese study in which BHA had produced forestomach tumours in the rat. The Committee endorsed the opinion of an EC working party on BHA (October 1982) and emphasized that information should be obtained on whether BHA could produce epithelial hyperplasia in the oesophagus and/or glandular stomach of species without a forestomach, or if its action was specific for the rodent forestomach.

Since that time more work has been carried out to resolve the above questions and to determine the mechanism for the action of BHA, and whether or not BHA is genotoxic.

The previously available long-term studies in rats were carried out rather a long time ago and it is possible that the study designs may not have taken the same account of forestomach lesions as was the case in the more recent Japanese studies. Also the highest dose used previously was 0.5% BHA in the diet. In Ito's study 2% BHA in the rat diet

produced tumours but 0.5% did not, although hyperplasia was present. In a similar study carried out by Tomii and Aoki a few forestomach tumours were found at 1% dietary level of BHA. Because of the steep dose response curve these authors questioned whether there may be a threshold for the tumorigenic effect of BHA.

Many short-term studies have been carried out in several species to determine whether BHA's action is specifically on the forestomach epithelium, and whether there is a threshold for hyperplasia. Depending on the duration of the experiment, BHA has been shown to produce hyperplasia and/or tumours specifically in the forestomach of rats, mice and hamsters. The hyperplasia is reversible but the time taken for recovery depends on duration and level of dosage with BHA. The NEL for hyperplasia in the rat forestomach is 0.125% BHA in the diet.

In animals without a forestomach - guinea pig, dog, pig, monkey - BHA produced no histological effects (including no hyperplasia) in the oesophagus or glandular stomach. In gavage studies in the monkey, the mitotic index in the 'target' squamous epithelium of the distal oesophagus was raised at high dose levels, but not at 250 mg/kg bw.

The Committee concluded therefore that the action of BHA in producing forestomach hyperplasia and tumours in rodents may not be relevant for man.

Other data examined by the Committee included promotion studies and results of mutagenicity tests. BHA has been shown to have both inhibitory and promotional effects on tumour yield from treatment with known carcinogens - the inhibitory effect being stronger. Nearly all the available mutagenicity data were negative and BHA has not been demonstrated to be a genotoxic compound. This reinforced the Committee's view that the effects on the rat forestomach were not significant for assessing risks to human health.

The Committee had previously noted the lack of a multigeneration study. However, in a number of (1 generation) reproduction studies with rats, mice and monkeys, at dose levels of 50 mg/kg bw or higher no effects were observed except on the behaviour of mice. Teratogenicity studies were all negative. The Committee therefore agreed that a temporary ADI for BHA was now acceptable.

The Committee concluded that the production of rodent forestomach tumours by BHA was not a manifestation of genotoxicity; and that in addition to being an effect with a threshold, the preceding hyperplasia may not be of relevance for man. Further reassurance was to be found in the results of studies in species without a forestomach. In setting an ADI the Committee took into account that :

(a) the NEL in a 90-day study for production of hyperplasia in the rat forestomach (62.5 mg/kg bw). Given the evidence of lack of effect in more relevant species, the Committee considered that a safety factor of 100 was adequate;

and

(b) the NEL of 250 mg/kg bw previously determined in a long-term chronic toxicity feeding study - on the basis of which JECFA had established a temporary ADI of 0-0.5 mg/kg bw (using a safety factor of 500).

The Committe established a temporary ADI of 0-0.5 mg/kg bw.

The Committee noted that the actual (estimated) daily intake of BHA is far less than that allowed by the temporary ADI. The Committee wishes regularly to review the status of BHA, and information from ongoing studies and on actual intakes.

Butylated Hydroxytoluene (BHT)

The Committee has reviewed all available studies on BHT, including metabolic data from several species including man, mutagenicity studies, carcinogenicity studies in rats and mice, and special studies on the thyroid, blood and postnatal development and behaviour.

A recent two-generation feeding study in the rat showed an increased incidence of hepatocellular adenomas and carcinomas at the two higher dose levels (100 and 250 mg/kg bw). All the tumours were first noted after two years, the majority at termination between 141 and 144 weeks; and the survival of control animals was markedly poorer than in those fed BHT. Previous feeding studies in rats have not shown such carcinogenic effects. The Committee's view that the recent study suggests a threshold for carcinogenesis (related to liver enzyme induction) was reinforced by the results obtained from mutagenicity testing, with an overall lack of evidence of genotoxic effect in in vivo systems. Like other antioxidants BHT can exhibit promoting or inhibiting effects on carcinogenesis. BHT does not cause hyperplasia in the rat forestomach. Effects on mitotic rate are diverse.

Since the NEL demonstrated for carcinogenesis was higher than that obtained for other toxicological effects, the ADI was determined from the latter.

The information available from a 90-day feeding study in the rat indicated there was a dose-related increase in relative thyroid weight of 40% and 67% in the 500 and 5 000 ppm BHT groups respectively; iodine uptake and the height of follicular epithelial cells were increased at 5 000 ppm (not measured at 500 ppm). However, blood levels of tri-iodothyronine and thyroxine at both dietary levels were unchanged, and the increase in the half-life of thyroxine seen early in the study was only transient. In the in utero exposure rat carcinogenicity study, a 5% reduction in offspring body weight at weaning was seen in those reared by dams fed 25 mg/kg bw, equivalent to approximatey 500 ppm BHT in the diet. Since these effects on the thyroid and on offspring body weight were found at the lowest levels tested in these particular studies, NEL have not been clearly established. In view of these data, and the nature of the effects observed, it is reasonable to assume the likely NEL for thyroid and offspring body weight changes will be about 5-fold lower than the lowest-observed-effect level, i.e. about 100 ppm in the diet.

A series of haematological studies has shown that some, but not all species tested show haemorrhaging and/or a reduction in the prothrombin index after dosing with BHT. The mechanisms by which BHT brings about these effects appear to be several but the major effect is a reduction in activity of certain clotting factors, principally those which are Vitamin K-dependent. The most susceptible species for haemorrhagic effects appears to be the rat, and for this species the NEL for transient reduction (1 week's duration) of the prothrombin index was 85 ppm in the diet, and for persistent reduction (4 weeks' duration), 2 500 ppm in the diet.

Taking all these effects into account, the Committee considered that the likely NEL for BHT is approximately 100 ppm in the diet, equivalent to an intake of about 5 mg/kg bw/d. In view of the nature of the effects, a safety margin of 100-fold is appropriate to establish an ADI of 0-0.05 mg/kg bw based on thyroid, reproduction and haematological effects in the rat.

Tertiary-butylhydroquinone (TBHQ)

The Committee previously expressed its opinion on TBHQ in December 1981 when it drew attention to the lack of adequate data on which to assess the genotoxic and carcinogenic potential of this antioxidant. The Committee, therefore, did not establish an ADI at that time.

Since then, further *in vitro* and *in vivo* mutagenicity data have become available which do not exclude the possible genotoxicity of TBHQ.

The Committee therefore restated the need for an adequate carcinogenicity study and also requested an *in vivo* mutagenicity study of germ cell effects.

The Committee did not establish an ADI for TBHQ, and the substance is not acceptable for use as an antioxidant to food.

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The members are independent persons, highly qualified in the fields associated with medicine, nutrition, toxicology, biology, chemistry, or other similar disciplines.

The Secretariat of the Committee is provided by the Directorate-General for Internal Market and Industrial Affairs of the Commission. Recent Council directives require the Commission to consult the Committee on provisions which may have an effect on public health falling within the scope of these directives.

The present report relates to the opinion of the Scientific Committee for Food on the safety of antioxidants

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