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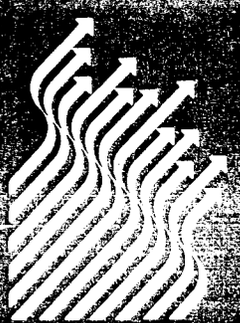
food — science and technologies

Reports of the Scientific Committee for Food

(Twenty-sixth series)



Report

EUR 13913 EN

Commission of the European Communities

food — science and techniques

Reports of the Scientific Committee for Food

(Twenty-sixth series)

Second series of food additives of various technological functions

(Opinion expressed on 19 October 1990)

Nitrates and nitrites

(Opinion expressed on 19 October 1990)

Health aspects of the release of lead from capsules for wine

(Opinion expressed on 7 December 1989)

Toxicity of lead and cadmium in ceramics

(Opinion expressed on 7 December 1989)

Guidelines for presentation of data for toxicological evaluation of a substance to be used in materials and articles intended to come into contact with foodstuffs

(Version adopted officially by the Scientific Committee for Food on 18 May 1990)

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Report of the Scientific Committee for Food on a Second Series of Food Additives of Various Technological Functions

(Opinion expressed 19 October 1990)

Terms of reference

To advise on the safety of a second series of food additives of various technological functions.

Background

In its 25th report series [1] the Committee evaluated a first series of food additives, previously referred to unofficially as "miscellaneous additives", not yet covered by current Community provisions but included in the framework directive on food additives. At that time the Committee decided to postpone the evaluation of **glazing agents, flour treatment agents and bulking agents** to a later stage in order not to delay the publication of its opinions.

This report deals with those substances falling within the above-mentioned groups, for which the Committee has now received toxicological data. Furthermore, the Committee considered it expedient to include also some substances, falling within the scope of existing directives, which have been evaluated fairly recently but had not yet been reported. Among these are some **preservatives, emulsifiers and antioxidants**. The present evaluations are not to be regarded in isolation but in connection with previous published reports concerning these groups of additives (preservatives: 1st, 2nd, 4th, 6th, 9th and 11th series; emulsifiers: 7th, 8th, 13th, 15th and 21st series).

Current review

Flour Treatment Agents

The Committee has previously given its opinion on 3 substances used also as flour treatment agents. These are sulphites (5th and 11th report series), ascorbic acid (22nd report series) and cysteine (25th report series). The present report includes the evaluations of a further 5 substances. Of these **potassium bromate and ammonium persulphate** were found **not acceptable** on the basis of presently available data, while the existing data on the safety of flour treated with **chlorine, chlorine dioxide and azodicarbonamide** were not sufficiently complete for a full evaluation.

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[1] *Reports of the Scientific Committee for Food* (1990), 25th series, EUR 13416 EN.

In the case when only insignificant residues remain after use, the main concern of the Committee related to the likely formation of reaction products during treatment. Therefore more analytical information on the nature of these reaction products and further relevant tests on the treated flour were requested.

Glazing Agents

The Committee was presented with a list of numerous substances which had been requested for inclusion in the Community list of food additives. However for most of them only very scarce information on specifications, toxicity data and on current as well as proposed uses was available. The Committee was able to accept the temporary continued use for only 6 of the proposed substances, for which the available toxicity data, their long established use without apparent adverse effects, and the expected limited intake when used as glazing agents provided some reassurance of safety.

For full acceptance as glazing agents and for acceptance of other uses which may increase the intake significantly the Committee would require the submission of supplementary toxicity data as set out in the guidelines for the safety evaluation of food additives [2] by 1995.

The Committee considered **mineral hydrocarbons not acceptable** as food additives until adequately performed tests enable it to establish acceptable daily intakes for properly specified products.

Preservatives

Dimethyldicarbonate has been requested for use as a sterilising agent in soft drinks. As this substance is fully degraded during use the Committee evaluated data relating principally to tests performed with treated soft drinks and with known reaction products. In the light of the information submitted the Committee considered this treatment **acceptable** at the proposed use levels.

Nisin, propionic acid and boric acid have been in use as permitted preservatives for many years but the Committee has not previously published an opinion on them.

Emulsifiers, stabilisers, etc.

The Committee has evaluated three gums of which two had not been previously reported on.

In previous evaluations of food additives falling into this class the Committee noted that the highest feeding levels which could be tested satisfactorily, were frequently also the no-adverse-effect levels. In addition, the use levels required to obtain the desired technological effects are of a size which would ensure an adequate safety margin between the potential daily intake and the likely no-adverse effect level for man. The Committee therefore **found it unnecessary to specify a numerical ADI**. This assessment should be considered in connection with the usual use levels quoted in the monographs in Annex I. The Committee is aware that gums of a similar nature are used for other purposes, e.g. slimming diets. The efficacy for such uses has not been evaluated by the Committee, nor does the safety evaluation for use as food additives cover such uses. The Committee intends to address these matters at a later stage.

Antioxidants

The two antioxidants evaluated in this report have been evaluated previously. In 1987 (22nd series) **isoascorbic acid** was considered **not acceptable** because an undesirable interaction with ascorbic acid could not be excluded. New data submitted to the Committee have given

[2] Report of the Scientific Committee for Food on guidelines for the safety assessment of food additives (1980), 10th series, EUR 6892 EN.

reassurance that intakes within the ADI will not interfere with the absorption of or biological activity of dietary ascorbic acid.

Calcium disodium EDTA was allocated an **ADI of 2.5 mg/kg** bw. in 1977. Because of concerns about a possible antinutrient activity the Committee was asked to review this substance. The Committee **confirmed the ADI** and is satisfied that, provided intakes remain within the ADI and the substance is not used in food supplying the major part of dietary minerals, the mineral binding properties of this substance have no significance for health.

Other additives

Polydextrose is used in sugar-free products to replace the bulking properties of sugar and as a stabilizer. The Committee considered this use as **acceptable** from the toxicological point of view. However conflicting results exist concerning the energy value of this substance and the Committee therefore did not endorse at present the claim of 1 kcal/g polydextrose.

Triethylcitrate and glyceryl mono-, di- and triacetate have been evaluated previously as carrier solvents (11th report series) and have now been judged **acceptable** also as food additives. **Polyvinylpyrrolidone and polyvinylpolypyrrolidone** are used as excipients and processing aids, uses which do not fall strictly under the scope of the framework directive for food additives. The Committee considered these uses **acceptable** from a toxicological point of view, taking into account the limited potential intake.

The Committee reviewed **maltol** when preparing its reports on a first series of food additives of various technological functions but postponed a decision until the results of mutagenicity tests could be fully evaluated. The Committee has now allocated an **ADI of 1 mg/kg bodyweight** to this flavour enhancer.

Summary table of evaluations

Flour treatment agents

- Potassium bromate	Not acceptable
- Chlorine)	
- Chlorine dioxide)	Evaluation postponed
- Azodicarbonamide)	
- Ammonium persulphate	Not acceptable

Glazing agents

- Beeswax)	
- Candelilla wax)	
- Carnauba wax)	Temporarily acceptable
- Shellac)	until 1995
- Montan acid esters)	
- Oxidised polyethylene waxes)	
- Mineral hydrocarbons	Not acceptable

Preservatives

- Dimethyldicarbonate (DMDC)	Acceptable for treatment of soft drinks and juices at levels up to 250 mg/l
- Nisin	ADI 0.13 mg/kg bw.
- Propionic acid	ADI not specified
- Boric acid	Acceptable only for real caviar

Emulsifiers, stabilisers, etc.

- Glycerol esters of wood rosin	Temporary ADI 0.5 mg/kg bw.
- Gellan gum)	
- Xanthan gum)	ADI not specified
- Tara gum)	

Antioxidants

- Isoascorbic acid	ADI 6 mg/kg bw.
- Calcium disodium EDTA	ADI 2.5 mg/kg bw.

Other additives

- Polydextrose	ADI not specified
- Triethylcitrate	ADI 20 mg/kg bw.
- Glyceryl mono-, di- and triacetate	ADI not specified
)	Acceptable as excipients
- Polyvinylpyrrolidone (PVP))	in sweetener and vitamin
- Polyvinylpolypyrrolidone (PVPP))	tabletting and as
)	processing aid
- Maltol	ADI 1 mg/kg bw.

For a more detailed description of the evaluations see Annex I.

Annex 1: Evaluation of the additives

Contents

1. Flour Treatment Agents

1.1 Potassium Bromate

This substance is used as an improver in flour for breadmaking at levels up to 50 mg/kg flour. The Committee was provided with information on metabolism, short-term studies in the rat, dog and monkey, and on long-term studies in rats and mice fed on bread made from flour containing potassium bromate. The Committee reviewed a further long-term study in rats with potassium bromate and several *in vitro* and *in vivo* mutagenicity studies. The new long-term study in rats showed reduced bodyweight gains, increased mortality and a treatment-related and dose-related incidence of renal and thyroid tumours in both sexes. Much of the published data on mutagenicity was inadequate, but the available data suggested that potassium bromate had clastogenic ability both *in vitro* and *in vivo*. On the basis of an analysis of the data the Committee concluded that potassium bromate is a genotoxic carcinogen.

A large proportion of bromate is converted to bromide during the manufacture of bread and limited analytical studies indicate that bromate residues are undetectable at normal treatment levels. Nevertheless, the Committee recommended that **the use of potassium bromate as a flour treatment agent should be discontinued** because of uncertainties about the possibility of bromate residues occurring in bread consumed by the public and in view of the likely industrial exposure of workers in bakeries, flour mills and other factories, and the likely exposure of some consumers to uncooked flour containing bromate.

1.2 Chlorine

This gas is applied to flour up to a level of 2500 mg/kg to make it suitable for manufacturing "high ratio" cakes with a high moisture and sugar content. There is inadequate analytical data on the identity of the reaction products of chlorine and flour, and the animal feeding studies suffer from a number of methodological deficiencies. These studies included 4 long-term studies in rats and mice fed cake made from chlorinated flour, a six month study in beagle dogs, a reproduction study in rats and short-term studies in rats on chlorinated flour, chlorinated lipids and lipids extracted from chlorinated flour.

In the 4 long-term studies no adverse effects were noted which could be related to chlorine treatment, except possibly anaemia. Neither were there any treatment-related adverse effects in the dog study or the reproduction study in the rat. Such effects as increased bodyweight, glomerulonephritis, renal calculi, an increased incidence of pituitary adenomas, and possibly increased lymphomas (one study only) were almost certainly attributable to the imbalance in nutrition consequent upon the very high percentage of cake in the diet, as similar effects were seen in the controls fed cake made from non-chlorinated flour. The effects reported in some studies in rats fed large amounts of very highly chlorinated flour or lipids included reduced bodyweight and increased liver and kidney weights without any accompanying histopathological changes. They are of doubtful relevance to the human consumer. The finding of mutagenic compounds produced from the reaction of food components with high concentrations of aqueous chlorine is difficult to relate to the reactions of gaseous chlorine.

While the available data provide no clear evidence that chlorine-treated flour is toxic and the absence of neoplasia in 4 long-term rodent studies on cake flour is reassuring, **more data is needed to provide adequate proof of safety**. Such data will need to include analytical studies to identify reaction products and to demonstrate the absence of toxic chlorinated compounds, studies on the mutagenicity of compounds in treated flour, and further animal feeding studies.

The Committee has seen proposals for 90-day feeding studies using extracts of cake made from chlorine-treated flour. While these could provide useful information it was very unlikely that such studies on their own could provide adequate reassurance on the safety of chlorine treatment.

1.3 Chlorine dioxide

This gas is used at levels up to 30 mg/kg flour as an improver for flour in breadmaking. There are limited toxicological data on chlorine dioxide as a flour treatment agent. Most of the animal feeding studies using chlorine dioxide-treated flour in rats, rabbits, dogs and monkeys are inadequate, the only observed effect being reduced weight gain if high concentrations of chlorine dioxide were used. The only adequate long-term studies in rats and mice used chlorine dioxide at low treatment levels and in combination with other treatment agents. The adverse effects seen were also found in animals fed on untreated bread or bread made with other improvers.

The analytical data on reaction products and on the fate of chlorine dioxide in flour are inadequate, although chlorine dioxide is said to be completely reduced to chloride. There is some evidence that chlorine dioxide reacts with flour components including lipids, proteins and tocopherol. Aqueous solutions of chlorine dioxide, and its degradation products chlorite and chlorate, are bacterial mutagens and mutagenic *in vivo* but only by the intraperitoneal route. They also have toxic effects in animals. These findings are difficult to relate to the reaction of gaseous chlorine dioxide with flour.

In order to allow safety assessment **more data is needed** from further analytical, mutagenicity and animal studies on chlorine dioxide treated flour. In view of the mutagenicity of chlorine dioxide, long-term animal studies on this compound might be needed if residues of chlorine dioxide or related compounds are present in treated flour.

1.4 Azodicarbonamide (ADA)

This substance has been used in flour as an oxidising improver in breadmaking at levels up to 45 mg/kg flour. In this process ADA is converted to biurea. The Committee was informed about earlier studies involving acute and subacute administration to rats and dogs and a one year feeding study in rats on biurea. The Committee reviewed a study in rats on metabolism of radiolabelled ADA and *in vitro* as well as *in vivo* mutagenicity studies. These latter provided evidence that ADA is a direct acting bacterial mutagen, though there is no evidence for mutagenic activity *in vivo*. The toxicological data on ADA and biurea are generally adequate to provide reassurance on the safety of this agent, provided it can be shown that ADA residues are not present in treated flour and that conversion to biurea is complete. The available analytical data are inadequate in this respect, but the Committee was informed that further analytical studies were now in progress. **A final decision was deferred** until the results of these studies are available.

1.5 Ammonium persulphate

This substance has been used as an oxidising improver in flour for breadmaking at levels up to 50 mg/kg flour. When ammonium persulphate was evaluated by JECFA in 1965 no acceptable treatment level could be estimated in the absence of adequate toxicological data and long-term studies on flour treated at several dose levels with ammonium persulphate as well as bread baked from it were requested. As such studies or other studies sufficient to evaluate its safety in use had not been submitted, and noting that no Member State authorizes its use, the Committee **could not recommend that this substance be included** in the Community list of permitted flour treatment agents.

2. Glazing agents

2.1 Beeswax

Beeswax consists essentially of esters of high molecular weight monohydric alcohols and long straight chain fatty acids. It is used as a glazing agent for external surfaces. The Committee reviewed acute toxicity studies, dermal toxicity studies in rats and rabbits, and local implantation studies in the cervix of mice. Because of the paucity of experimental toxicological data the Committee was unable to establish the safety of this compound but considered the continued use as glazing agent at present levels **temporarily acceptable** until further toxicological data and technical data on use have been provided.

2.2 Candelilla wax

This wax is composed essentially of hydrocarbons and esters. It is used as a glazing agent and as an ingredient of chewing gum base. The Committee was informed of short term studies in rats and dogs and of long term studies in mice and rats with candelilla wax as a component of various chewing gum bases. The Committee reviewed acute oral toxicity studies and dermal teratogenicity studies. None of the studies reported any adverse treatment-related toxicological findings. Based on the available data the Committee was unable to establish the safety of this compound but considered the continued use as glazing agent at present levels **temporarily acceptable** until further toxicological data and technical data on use have been provided.

2.3 Carnauba wax

This wax is composed essentially of aliphatic and cinnamic aliphatic esters. It is used as a glazing agent.

The Committee reviewed a 90-day study in rats, a one generation reproduction study in rats in which the F_1 generation was further treated for 90 days, a 28 weeks study in beagle dogs and *in vitro* mutagenicity studies. No adverse treatment-related toxic effects were reported in any of the studies. Although the available data are incomplete the Committee **accepted temporarily** the continued use of this compound at present levels until further toxicological data and technical data on use have been provided.

2.4 Shellac

This substance contains aliphatic and sesquiterpenic acids and is used to cover certain confectionery.

The Committee was informed of studies on acute toxicity, on subchronic studies in rats, a one generation reproduction study in rats as well as an *in vitro* mutagenicity study. Although the available data are inadequate to establish the safety of the compound the Committee **accepted temporarily** its continued used at present levels until further toxicological data and technical data on use have been provided.

2.5 Montan acid esters

Montan acid esters are produced by oxidative bleaching of natural montan wax - a fossil palm wax - followed by esterification of the montan acids with ethylene glycol and/or 1,3-butylene glycol and/or partial saponification with calcium hydroxide.

Acute studies in the mouse, subchronic data in the dog, and chronic toxicity studies in the rat on Hoechst Wax E, Wax KPS and Wax OP did not show any compound-related effects at dietary levels up to 5 %. The studies had certain inadequacies. Wax E was not mutagenic in a microbial reverse mutation test.

The Committee **accepted temporarily** the continued use of these 3 products at present levels (maximum 140 mg/kg fruit) for the surface treatment of citrus fruit until 1995.

2.6 Oxidised polyethylene waxes

These substances are produced by partial oxidation of polyethylene wax or linear polyethyelene with air.

Data on subchronic toxicity in the rat for Hoechst Wax PED 522 and Wax PED 135 show no compound-related effects at dietary levels up to 5 %.

The Committee **accepted temporarily** the continued use of these 2 products at present levels (maximum 140 mg/kg fruit) for the surface treatment of citrus fruit until 1995.

2.7 Mineral hydrocarbons

The Committee considered the available toxicological data which comprise metabolic studies, subchronic dietary and gavage studies, 90-day studies on various white mineral oils, several lifetime feeding studies in rats of liquid, semi-liquid and solid mineral hydrocarbons, dermal carcinogenicity studies in mice, reproducton and teratogenicity studies in rats on specific hydrocarbons as well as *in vitro* and *in vivo* mutagenicity studies. It reviewed specifically two recent 90-day feeding studies which showed mineral oil deposition in spleen, liver and lymph nodes together with histological and haematological abnormalities. A no-effect-level had been determined in one of the studies, but this study was incomplete as no haematological investigations had been performed. The rest of the toxicology data base was inadequate, as, in particular, no adequate long term, mutagenicity and reproductive toxicity studies had been performed. The Committee also noted that there were unresolved problems over the specifications for these compounds.

The Committee also noted the long history of medicinal use of these compounds in humans without reported adverse health consequences. This gave some degree of reassurance, but the human studies had not been designed to address the problem of possible toxic or adverse effects of specific mineral oil products.

The Committee concluded that the available data did not permit an ADI to be set, and that there was no toxicological justification for the continued use of mineral hydrocarbons as food additives. However there was no evidence of an acute health hazard which would warrant urgent action to change the present pattern of use of these compounds in food.

On the basis of the two 90-day studies the Committee set a **temporary TDI of 0.005 mg/kg bw/day** for conventionally (oleum) treated mineral oil and **0.05 mg/kg bw/day** for hydrogenated oil to cover residues in food arising out of use of mineral oil hydrocarbons in food packaging materials. Continued use for this purpose is conditional on new short term studies on well specified mineral oils being performed, followed by long term studies completed by 1995.

3. Preservatives

3.1 Dimethyldicarbonate (DMDC)

This substance has been requested for use in soft drinks and fruit juices but the Committee did not consider the question of technological need. DMDC is added at levels of 125-250 mg/l during bottling. The substance breaks down mainly into methanol and carbon dioxide together with a number of products in minute quantities due to side reactions with components of soft drinks or fruit juices.

The levels of methanol resulting from the use of DMDC are similar to or less than those occurring naturally in many fruit juices or alcoholic beverages, and are not toxicologically significant. The

Committee considers that of the side reaction products formed only methylcarbamate from reaction with ethyl alcohol could be a possible cause for concern.

The Committee reviewed data on the spectrum of antibiotic activity of DMDC and adequate data on acute toxicity, subchronic studies in rats and dogs, reproduction and teratogenicity studies as well as long term studies in rats on orange juice and alcoholic beverages treated with DMDC. No treatment-related adverse effects were noted.

Methylcarbamate was examined in metabolic studies and adequate data were provided on acute toxicity, subchronic studies in mice and rats as well as long term studies in mice and rats. Methylcarbamate produced hepatocellular carcinomas in one strain of rats at high dose levels but had no such effect in another strain of rats and in mice. Several *in vitro* and *in vivo* mutagenicity studies showed methylcarbamate to be a clear-cut non-genotoxic agent. The residues of methylcarbamate in soft drinks are less than 20 µg/l and there is a safety margin of several orders of magnitude between possible consumer intakes and the dose producing carcinogenic effects in one strain of rats. Under these circumstances the Committee considered that the presence of methylcarbamate at this level does not pose a risk to human health and there is **no toxicological objection** to the use of DMDC in soft drinks at the levels proposed.

3.2 Nisin

This substance is a polypeptide antimicrobial agent useful for inhibiting the outgrowth of bacterial spores in pasteurised foods. The Committee was provided with a review by JECFA in 1968 of studies on acute toxicity, subchronic studies and long term studies in mice and rats, and a reproduction study in rats. The Committee reviewed a further reproduction and teratogenicity study as well as *in vitro* and *in vivo* mutagenicity studies. The available data on genotoxicity and carcinogenicity, though limited by present-day standards, have not shown any adverse treatment-related effects. Based on the recent reproduction study the Committee decided to allocate an **ADI of 0.13 mg/kg bw** for a product with a potency of 40.000 units/g.

3.3 Propionic acid

This fatty acid and its sodium and calcium salts are used as preservatives in certain bakers' wares and sliced bread. The Committee was provided with a review by JECFA in 1973 of metabolic studies, data on acute toxicity, short term studies in rats and rabbits, and a long term study in rats using bread baked with propionic acid. None of these studies showed any treatment-related toxicological findings. The Committee reviewed recent 90-day studies with a recovery phase with propionic acid and calcium propionate in beagle dogs, short term feeding studies in rats, a 90-day feeding study with a recovery phase in rats, a long term study in rats extending over 1 year, and a lifespan study in rats, studies on teratogenicity and *in vitro* and *in vivo* mutagenicity studies. There was no evidence for a genotoxic potential. The lifespan feeding study in rats produced hyperplastic and carcinomatous lesions in the forestomach and some proliferation in the glandular stomach. Forestomach lesions in the short term studies were largely reversible, and similar lesions were seen with other short chain fatty acids. The diffuse hyperplastic mucosal changes in the oesophagus of dogs were fully reversible and were not induced by calcium propionate.

On the basis of the toxicological evidence reviewed the Committee **sees no adverse health consequences** to man from the present uses of propionic acid as a food additive. In order to evaluate the effects of this food additive comparative studies with other closely related short chain fatty acids and their salts should be performed.

3.4 Boric acid

This substance was evaluated by the Committee in 1979. The then available data comprised a review by JECFA in 1962 listing metabolic information, short term studies in rats, studies using parenterally administered boric acid in dogs and cases of human poisoning as well as studies in adults. The compound is nephrotoxic and may accumulate. The Committee reviewed a long term

study in rats which confirmed some accumulation in various organs. The Committee had earlier agreed that the use of boric acid should be strictly limited to the preservation of real caviar. In 1988 the Committee reviewed newer data including studies on acute toxicity, 90-day studies in rats and dogs, and a long term study in mice showing testicular atrophy as the main toxic effect. Bacterial mutagenicity tests were negative. The Committee endorsed the earlier opinion that boric acid and its salts were **toxicologically acceptable** only for use as preservative for real caviar.

4. Emulsifiers, stabilisers etc.

4.1 Glycerol esters of wood rosin

The basic rosins used for production of the glycerol esters are wood rosin, gum rosin and tall oil rosin which have all been tested in acute toxicity studies, 90-day studies and 2-year studies in the rat and the dog. A 90-day rat feeding study on Ester Gum 8 D indicates that this ester is qualitatively similar in effect to the parent rosin (wood rosin). The mutagenicity tests on Ester Gum 8 BG show absence of genotoxicity. Components of the rosin have been examined for metabolic behaviour. Assuming that Ester Gum 8 BG is the same product as Ester Gum 8 D and provided there is assurance that the only rosin present in this substance is wood rosin, the Committee allocated a **temporary ADI of 0.5 mg/kg bw** based on the no-effect-level in the long term rat study of 0.2% equivalent to 100 mg/kg bw. The safety factor applied was 200. The ADI remains temporary pending the results of a new 90-day study in the rat performed according to present-day standards and using a well specified commercial product.

4.2 Gellan gum

Gellan gum is a polysaccharide gum of high molecular weight produced by the fermentation of a carbohydrate by *Pseudomonas elodea*. It is intended for use as gelling agent and to some extent as a stabilizing and thickening agent in concentrations typically ranging from 0.1% to 1%.

The Committee has examined the extensive toxicological dossier which contains data on metabolism, acute toxicity studies, subchronic studies in rat, dog and monkey, a two generation reproduction and teratogenicity study in rats, long term studies in rats and mice, and *in vitro* studies on mutagenicity. Based on these data and the above mentioned use levels it was decided to allocate an **ADI not specified**. This evaluation does not cover other uses as for example for specific dietary or medical purposes. The specification of the substance should exclude the presence of viable *Pseudomonas elodea*. The Committee's earlier recommendation for the development of a more sensitive and more specific analytical method has now been complied with.

4.3 Xanthan gum

The Committee endorsed in its 7th Series of reports the ADI of 10 mg/kg bw. established by JECFA on the basis of available toxicological information. The latter consisted of studies on metabolism, acute toxicity, short term studies in rat and dog, a three generation reproduction study in rats, and long term studies in rat and dog as well as observations in man. The Committee was also informed about the nature of the nitrogenous constituents of xanthan gum.

As the highest possible feeding level was also the no-effect-level (NEL), the Committee considered it justified not to apply the 100 fold safety factor. The Committee was informed that levels in the range of 1-5 g/kg in foods and 0.5 g/l in beverages are usually adequate to obtain the desired technological effects. Based on this the Committee decided to change the **ADI** to **not specified.**

4.4 Tara gum

The Committee was supplied with information on metabolism, digestibility and caloric value studies, short term studies in mice, rats and dogs, a three generation reproduction and

teratogenicity study in rats, and long term studies in the mouse and rat. The substance was allocated an ADI not specified by JECFA in 1986 on the basis of this information. The Committee was supplied with the results of a new digestibility study. Accepting the evaluation of JECFA the Committee allocated an **ADI not specified** based on the use levels presented which ranged from about 0.5 % to 1 %.

5. Antioxidants

5.1 Isoascorbic acid

The Committee reviewed an extensive data base including studies on metabolism, competition with ascorbic acid, acute toxicity studies, short term studies in mouse and rat, long term studies in mouse, rat and dog, teratogenicity studies in mouse and rat, extensive mutagenicity studies, and studies in ascorbic acid-deficient humans. The Committee established an **ADI of 6 mg/kg bw.** calculated as isoascorbic acid based on the long term study in rats and the satisfactory agreement of these findings with the reported human nutritional experience.

5.2 Calcium disodium EDTA

In formulating its advice on the acceptability of $CaNa_2$ EDTA as a chelating agent in 1977 the Committee reviewed data on metabolism, acute toxicity studies, short term toxicity studies in rat and dog, and a long term study in rats and established an **ADI of 2.5 mg/kg bw.**. The Committee reconfirmed its advice in 1985 as no evidence had been submitted requiring the Committee to review the already established ADI. In arriving at this advice the Committee also reviewed some recent studies in rats on the teratogenicity of EDTA and its salts.

6. Other additives

6.1 Polydextrose

Polydextrose exists in a slightly acid and a neutral form (A and N) and is used as a bulking agent to replace sugar. The Committee has reviewed the submitted reports on toxicological and metabolic studies. The substance showed no toxic effects in acute, subacute or chronic studies in three species of animal at levels equivalent to 10 % of the diet. It is poorly absorbed but a fraction is metabolized by the gut flora primarily to carbon dioxide and volatile fatty acids. There are conflicting results from studies estimating the energy value. The Committee has been informed of studies designed to resolve this question and decided to postpone the advice on energy value until the results of these studies are available. Large doses of polydextrose exert a laxative effect with a mean laxative threshold of 90 g per day or 50 g as a single dose. Based on the available data the Committee allocated an **ADI not specified** pointing out that while considering appropriate levels for the use of polydextrose the laxative effect should be taken into account for the substance alone or in combination with other substances having a similar osmotic action (e.g. the polyols).

6.2 Triethylcitrate

This substance is used as a carrier solvent and as an extraction solvent. The Committee agreed in 1981 with the temporary ADI of 10 mg/kg bw. established by JECFA in 1979 on the basis of acute toxicity studies, short term studies in rats, cat and dog, and one long term study in the rat which was however not fully adequate by present-day standards. The compound is hydrolysed *in vitro* into its acid and alcohol moieties of well known metabolic fate in man. The compound was also non-mutagenic in the microbial systems tested. At that time the Committee considered this

substance temporarily acceptable for use as solvent for food but required adequate evidence of *in vivo* hydrolysis.

The requested additional data showed that such hydrolysis would occur. The Committee therefore agreed with the **ADI of 20 mg/kg bw.** established by JECFA in 1984.

6.3 Glyceryl mono-, di- and triacetate

These esters were evaluated by JECFA in 1975, 1976 and 1980 on the basis of *in vitro* hydrolysis data and acute toxicity studies. A group ADI not specified for glycerol and the three acetate esters was established. The Committee reconsidered this information and present existing knowledge about their metabolism and agreed with the **group ADI not specified** established by JECFA.

6.4 Polyvinylpyrrolidone (PVP)

This polymer is used as an excipient in vitamin and sweetener preparations at use levels of a few percent, thus resulting in very small intakes. The Committee was provided with information on metabolism, absorption, reticulo-endothelial system (RES) storage, acute toxicity, short term studies in rat, cat and dog, long term feeding studies in rat and dog, teratogenicity studies, *in vitro* mutagenicity studies, a study of the effects on the canine immune system, data on the current levels of the contaminant hydrazine, and observations in man. JECFA established an ADI of 50 mg/kg bw. in 1987. The Committee considered PVP **toxicologically acceptable** for the uses mentioned above on the basis of the summary data published by JECFA. If other uses in the future should significantly increase the potential intake the Committee would wish to review the original data.

6.5 Polyvinylpolypyrrolidone (PVPP)

This insoluble polymer is used as a disintegration aid in tabletting and as a processing aid in wine production. The Committee was provided with information on metabolism, short term studies in rats and dogs, and teratogenicity studies in rats, on the basis of which JECFA established an ADI not specified in 1983. Based on this information the Committee found the substance **toxicologically acceptable** for the above uses in view of the expected low exposure. If other uses should significantly increase the potential intake the Committee would wish to review the original data.

6.6 Maltol

The available biochemical data point to extensive metabolisation and rapid urinary excretion of conjugates common to phenolic compounds. Several adequate short-term and long-term studies as well as reproduction and mutagenicity studies were available. There was no indication of any carcinogenic effect but some indication for a genotoxic potential. The Committee therefore established an **ADI of 1 mg/kg bw.**

Annex 2

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Report of the Scientific Committee for Food on Nitrate and Nitrite

(Opinion expressed on 19 October 1990)

1. Terms of reference

To review the safety of nitrites and nitrates when used as food additives.

2. Background

Nitrate, nitrite and N-nitroso compounds have been the subject of many review papers and monographs in recent years:

- IARC monograph n° 4 (1974)
- Environmental Health Criteria n° 5 (WHO 1977);
- IARC monograph n° 17 (1978);
- G. Eisenbrand, N-nitroso Verbindungen in Nahrung u. Umwelt, 1981;
- NFA, Sweden, Nitrates, nitrites & N-nitroso compounds, 1981;
- Health Effects of Nitrate, Nitrite & N-nitroso Compounds, NAC USA, 1981;
- Alternatives to the Current Use of Nitrite in Foods, NAC USA, 1982;
- Deutsche Forschungsgemeinschaft, Das Nitrosamin-problem, 1983;
- Speijers et al., Integrated Criteria Document, Nitrate Effects, RIVM Rep., Bilthoven 1987;
- UK MAFF Food Surveillance Paper n° 20, 1987;
- Ecetoc Tech. Rep. n° 27, 1988;
- R. Walker, Working Paper prepared for the EEC, 1988 (published as "Nitrates, Nitrites and N-nitroso compounds, a review of the occurrence in food and diet, and toxicological implications", Food Additives & Contaminants, 1990);
- IARC International Symposia on N-nitroso Compounds, Lyon, 1989.

The present opinion is based mainly on these reviews.

Estimates of dietary exposure to nitrate indicate that the major source is vegetables which, in general, contribute more than 75 % of total dietary intake. However, in some areas drinking water

may make a major contribution. Intakes from food additive use of nitrates are much smaller. Mean nitrate intakes from all sources in many Western countries have been estimated to be well within the previously established ADI of 5 mg/kg bodyweight (as $NaNO_3$), although individual consumers may exceed this level. Dietary exposure to nitrites is normally very low, commonly less than 2 mg/d and usually less than 5 mg/d per capita (less than 0.1 mg/kg bw.). A significant further exposure might arise from saliva in which nitrite levels may attain 5-10 mg/l.

A number of estimates of dietary intakes of volatile nitrosamines have been made. Most recent estimates in the UK (MAFF 1987) indicate that average daily intakes of nitrosopyrrolidine and dimethylnitrosamine are 0.1 µg/d and 0.6 µg/d respectively with extreme daily intakes up to twice these figures. Estimates of daily intakes in Germany averaged 1.2 µg/d (Spiegelhader, 1980). The data are inadequate to estimate the intake of non-volatile N-nitroso compounds.

3. Current review

3.1 Technological considerations

Because of the potential relationship between the use of nitrates and nitrites as food additives and the formation of carcinogenic nitrosamines, the Committee has obtained technological information on the use of nitrates and nitrites in meat products, cheese milk and fish products from invited experts in microbiology, food preservation and technology and from Member States of the Community. This information is summarized below.

3.1.1 Meat products

The Committee was informed that nitrite exerts an effect on several undesirable micro-organisms, *Clostridium botulinum* being the most important from a health point of view. The amount of nitrite needed is dependent on the initial level of contamination.

The amount added also has an effect on general shelf-life (preventing off-flavours). The Committee points out however that as nitrite does not have an inhibitory effect on some micro-organisms which may be present in the meat, e.g. *Listeria*, certain *Salmonella* and *Yersinia enterocolitica*, the organoleptic shelf-life should not be set for an unrealistically long period of time.

The Committee was informed that the minimum effective concentration of nitrite with respect to *Clostridium botulinum* depends on a number of factors including hygienic status, pH, water activity, concentration of other salts etc. Given the hygienic conditions achievable by hazard analysis critical control point (HACCP) techniques, 50-100 mg added nitrite (as sodium nitrite) per kg meat products may suffice for many purposes but some products may require higher concentrations up to 150 mg/kg. This would normally result in residue levels of less than 50 mg/kg.

It was pointed out to the Committee that these figures are lower than presently allowed in some Member States and the Committee therefore recommends that production methods should be improved gradually to be able to reach this goal consistent with adequate microbiological

requirements. When curing is performed under strictly controlled conditions there seems to be no need for the combined use of nitrate and nitrite. The content of nitrate *per se* is of no toxicological concern, but the bacterial reduction of nitrate to nitrite is uncontrollable and may sometimes give rise to high concentrations of nitrite with the possibility of increased formation of undesirable reaction products. However, it was recognized that under certain production conditions nitrate might act as a necessary reservoir for nitrite. The Committee would not oppose this continued use as long as it was restricted to defined products where the need can be demonstrated and in amount strictly limited to that necessary. Efforts should nevertheless be made to change production methods in order to reduce and, when feasible, to abandon the combined use of nitrate and nitrite.

The Committee underlines the importance of only using nitrite mixed with salt as this would anyway limit the amount of nitrite which can be added and prevent accidental poisoning through the addition of excessive quantities to foods.

3.1.2 Cheese

The Committee was informed that even under hygienic conditions some microbial contamination of milk cannot be totally avoided. If the cows have been fed silage, which is a major feed in some areas, this contamination includes bacteria such as *Clostridium tyrobutyricum.* Although of no health concern, these bacteria prevent the manufacturing of certain cheeses and some kind of measure is necessary to control the growth during the maturing of these cheeses. The information available to the Committee indicated that the addition of 150 mg nitrate (expressed as sodium salt) per litre of cheese milk is sufficient for this use and it will result in a content in the final product not exceeding 50 mg nitrate/kg. Nitrite is normally not found in amounts higher than 1 mg/kg. The Committee found this acceptable from a toxicological point of view and the potential intake of nitrate from this source is considered insignificant compared with the ADI.

Although a correlation between the addition of nitrate and the formation of volatile N-nitroso compounds in cheese has not been demonstrated, recent studies suggest a possible correlation between nitrate and the content of apparent total N-nitroso compounds (see below 3.2.3). For this reason the Committee recommends that the use of nitrate should be restricted to 150 mg in milk for cheese manufacture until the toxicological significance of these findings can be clarified. For control purposes it is also recommended that a maximum limit for residual nitrate is fixed at 50 mg/kg in the finished cheese.

For the same reason, and to support improvement of hygienic practices in general, the Committee wishes to encourage current endeavours to improve conditions to reduce the need for preservatives in cheese manufacture.

3.1.3 Fish

The Committee was informed that in the northern countries nitrate is sometimes used during the production of certain herring products with ingoing amounts of 500 mg nitrate (as sodium salt) per kg fish. The use is to prevent the growth of micro-organisms producing off-flavours during ripening but has no function in preventing growth of pathogens.

Although it has been demonstrated that the use of nitrate exerts the said effect and that the formation of volatile N-nitroso compounds is independent of added nitrate, the Committee felt that further investigations on the use of nitrate for the production of herring products are desirable.

3.2 Toxicological considerations

3.2.1 Nitrite

The acute toxic effects of nitrite include relaxation of smooth muscle, vasodilation and lowering of blood pressure, and methaemoglobinaemia. The LD_{50} is generally in the order of 100-200 mg/kg bw.

Nitrite given to experimental animals in drinking water causes a dose-dependent methaemoglobinaemia and histopathological changes in cardiac muscle, lung, liver, spleen and kidney. Pharmacological effects include vasodilation and sedation apparently independent of methaemoglobinaemia. Dose-related hypertrophy of the adrenal *zona glomerulosa* was seen in studies with potassium nitrite. Faetotoxic effects in reproduction studies are only observed at dose levels at which there is a frank maternal methaemoglobinaemia.

Nitrite is mutagenic in a number of *in vitro* assays against micro-organisms or cultured mammalian cells. Mutagenic effects were also observed in an *in vivo-in vitro* experiment using Syrian hamsters (Inai *et al.*, 1979). *In vivo* assays have been equivocal, both positive and negative results having been reported.

In several long-term studies on nitrite *per se*, no carcinogenic activity was detected in mice or rats (Inai *et al.*, 1979; Maekawa *et al.*, 1982; Lijinsky *et al.*, 1983). A review of an earlier study (Newberne, 1978) did not support the original conclusion that there was an increased incidence of lymphoid tumours in nitrite-fed rats and it was concluded that this study was also negative (FDA, 1980a,b).

In combination with amines or amides, the formation of carcinogenic N-nitroso compounds has been demonstrated to occur *in vivo* and to lead to tumour induction in long-term studies in mice, hamsters and rats, but only at levels of dietary nitrite much higher than those to which man is exposed in the diet, drinking water or saliva.

The no-effect level of sodium nitrite in long-term studies in rodents cannot be assessed precisely; a no-effect level in drinking water was established as 100 mg/l (equivalent to 5-10 mg/kg bw.) but the next higher dose level was ten times as great and caused a small increase in metHb to 5%. Estimates of the minimum effective dose for man based on methaemoglobinaemia are in the range of 1-8.3 mg/kg bw.. There is considerable experience of human exposure in clinical use in which no serious adverse effects were observed at levels substantially higher than those encountered in the diet. Certain sub-populations may be at higher risk from dietary nitrite; these include infants, pregnant women, individuals who are congenitally deficient in glucose-6-phosphate dehydrogenase and a rare group with an hereditary lack of NADH- or NADPH-methaemoglobin reductase activity in the erythrocyte.

An estimate of the Acceptable Daily Intake may be based on levels causing no toxicological effects in a 2 year study in rats (approximatively 10 mg/kg bw.) and on the no adverse effect levels in clinical use in humans (approx. 1 mg/kg bw./d).

Taking a safety factor of 100 for the animal no-observed-effect-level (NOEL) or 10 for the human data, the Acceptable Daily Intake is estimated as 0.1 mg/kg bw. (expressed as sodium nitrite). This ADI is not applicable to infants under 3 months of age. This ADI should be considered temporary pending clarification of the mechanism of the adrenal effects of potassium nitrite observed in a recent short-term rat study.

3.2.2 Nitrate

Nitrate *per se* has a very low acute toxicity and reported adverse effects result from its reduction to nitrite either before ingestion or *in vivo*. Controlled acute human exposure under clinical conditions indicates that increases in circulating metHb are only seen at daily dose levels of several grams in healthy adults, corresponding to about 50 mg/kg bw. or higher.

Experimental carcinogenicity studies on nitrate *per se* have proved negative (Sugiyama *et al.*, 1979; Lijinsky *et al.* 1973; Maekawa *et al.*, 1982) and realistic levels of dietary nitrate do not appear to lead to significant formation of volatile N-nitroso compounds nor of nitroso-amino acids. Rats receiving a diet adequate in protein did not show any increase in N-nitrosoproline (NPRO) excretion after inclusion of inorganic nitrate in the diet, and isotopic labelling studies have shown that most urinary NPRO was derived from endogenous nitrosating species and not from orally ingested nitrate.

Epidemiological studies have failed unequivocally to demonstrate a link between nitrate exposure and cancer incidence in populations exposed to higher than average nitrate intake either in the diet and drinking water, or occupationally. Similarly, epidemiological studies in populations with high and low cancer incidence have failed to demonstrate a link between cancer risk and nitrate intake.

No-effect levels in experimental studies on nitrate vary with the criteria used and what levels of circulating methaemoglobin are considered to be within the normal range. In the most recent two-year carcinogenicity study in the rat (Maekawa, 1982) the no-effect level for sodium nitrate was found to be 2500 mg/kg bw/d while in the older long-term study in the rat on which the previous ADI was based, the no-effect level of 500 mg/kg bw/day was the highest level tested.

Although there are differences between the rat and man in that the rat does not secrete nitrate in saliva with subsequent partial reduction to nitrite, the long term studies with nitrite administered to the rat in drinking water indicate that regular ingestion of nitrite at much higher levels than occur in saliva was without carcinogenic risk. Nevertheless, in view of these interspecies differences, the Committee considered it prudent to use a safety factor of 500 to calculate the ADI. Accordingly, an ADI of 5 mg/kg bw was established (based on the most recent rat study).

Since infants may be more likely to reduce exogenous nitrate to nitrite and are more sensitive to the acute effects of nitrite, nitrate should not be used as an additive in infant foods.

3.2.3 Nitrosamines and nitrosamides

Many nitrosamines and nitrosamides have been shown to be potent carcinogens in several species, including primates, so it may be assumed that they are carcinogenic for man. These compounds, including dimethylnitrosamine, diethylnitrosamine, nitrosopyrrolidine and nitrosopiperidine which have been identified in foods, are formed from nitrite and various nitrosatable amines. In addition it is known that non-volatile N-nitroso compounds may also be formed, in some cases in amounts exceeding those of volatile nitrosamines. Little is known of their occurrence or toxicological properties although some are known to be mutagenic.

The exposure, epidemiological and other data relating to dietary nitrosamines, provide no direct evidence that the current levels of nitrosamines present in the diet are hazardous to human health. From the foregoing, while it is clearly not possible to make precise quantitative estimates of risk, it is prudent to ensure that exposure to preformed nitrosamines in foods should be minimised by appropriate technological practices such as lowering the nitrite addition to foods to the minimum necessary to achieve the required preservative effect and ensure microbiological safety. Reducing the dietary levels of nitrite would additionally lower the possibility of nitrosation *in vivo* although, in this regard, the contribution made by salivary nitrite may be equally important. There appears to be a clear correlation between added nitrite levels in foods and the formation of volatile nitrosamines. While there appears to be no such clear correlation between added nitrate levels and the formation of volatile nitrosamines, further information is required about the potential involvement of nitrate in the formation of non-volatile N-nitroso compounds.

4. Summary and conclusions

The Committee has considered the use of nitrates and nitrites as food additives, in context with their intake from other sources. In the latter regard, pollution of the environment with nitrates represents a major public health problem. The Committee has also considered the formation of N-nitroso compounds in foods containing nitrates and nitrites, in context with the formation of nitrosamines in the human gastro-intestinal tract.

Intake data for nitrates, nitrites and N-nitroso compounds are not available for the Community as a whole, but in all areas studied it seems clear that:

(a) the use of nitrate as food additives makes a relatively small contribution to the total intake, the majority coming from vegetables and drinking water;

(b) intakes of nitrate and nitrite from food are generally well within the ADIs, except in areas where levels of nitrate in vegetables are high and levels in drinking water exceed Community standards;

(c) no direct toxic effects are therefore expected from food additive uses of nitrates and nitrites when used within the levels indicated in this report.

The situation is less clear-cut in the case of N-nitroso compounds. There are considerable problems in identifying and measuring the amounts of such substances in foods, except in the case of a few well-characterised volatile nitrosamines. The data available on those nitrosamines whose carcinogenic potential is known suggest that, at the level at which they have been detected in dietary

studies, any adverse health effects are likely to be small. However, the Committee is not in a position to make a quantitative assessment of risks from all N-nitroso compounds present in foods as eaten or formed by nitrosation in the human gastro-intestinal tract. The Committee therefore **recommends** that priority should be given to research on analytical methods, assessment of carcinogenic potency and of *in vivo* nitrosation which will permit a better assessment of the risks from N-nitroso compounds in food.

It would be prudent to reduce the levels of pre-formed nitroso compounds in the diet as far as possible. The Committee therefore **recommends** that exposure to preformed nitrosamines in food should be minimized by appropriate technological practices such as lowering levels of nitrite and nitrate added to foods to the minimum required to achieve the necessary preservative effect and to ensure microbiological safety. These levels of nitrite and nitrate should be the lowest achievable in accordance with the information provided to the Committee during the course of the present review.

The Committee **recommends** that further research should be carried out on the possibility of developing alternative preservatives and in the meantime, on methods of inhibiting the nitrosation reaction in foods.

The Committee underlines the importance of only using nitrite mixed with salt in meat production as this would automatically limit the amount of nitrite which can be added and prevent accidental poisoning through the addition of excessive quantities to foods.

The Committee has established an Acceptable Daily Intake (ADI) of 0-5 mg of **nitrate** per kg bw (expressed as sodium nitrate) and a Temporary Acceptable Daily Intake of 0-0.1 mg of **nitrite** per kg bw (expressed as sodium nitrite). The ADIs for nitrate and nitrite include human intake from all sources. Pollution of the environment with nitrate is a major public health problem, and this problem should remain on the agenda of the Committee as far as it relates to food.

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Opinion of the Scientific Committee for Food on the Health Aspects of the Release of Lead from Capsules for Wine

(Opinion expressed 7 December 1989)

Terms of reference

To give an opinion on the health hazards arising from the use of lead capsules on wine bottles.

Discussion

Analysis of wine poured from bottles sealed with lead capsules has revealed the occurrence of toxicologically unacceptable concentrations of lead in a proportion of the samples tested. Intake of small amounts of lead from food is unavoidable because of the ubiquitous presence of naturally occurring of lead in the environment. In addition to this, exposure to lead is increased further due to pollution. Efforts should continue to be made to reduce the intake of lead from food.

Accordingly, the Committee **recommends** that there should be no additional contamination of wine from the use of lead capsules.

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Opinion of the Scientific Committee for Food on the Toxicity of Lead and Cadmium in Ceramics

(Opinion expressed 7 December 1989)

Terms of reference

To give an opinion on the health hazards arising from the use of lead and cadmium in ceramics.

Discussion

At its 30th meeting in 1986, JECFA established a PTWI for lead of 25 µg/kg bodyweight in infants and children and at its 33rd meeting in 1989 it established a PTWI for cadmium of 7 µg/kg bodyweight.

The provisional tolerable weekly intake (PTWI) for lead was based on evidence that a mean total daily intake of 3-4 µg/kg bw. of lead by infants and children is not associated with an increase in blood lead levels. For the average infant agend 0-6 months the tolerable total daily intake would amount to 36 µg, while a small child aged 6 months-2 years could tolerate 54 µg as tolerable total intake. Assuming that about 50 % of the total daily intake of lead derives from food sources this would give a range of daily intake from food between 18 and 27 µg of lead.

The PTWI for cadmium was derived from estimated Cd accumulation over 50 years for adults. It recognizes that exposure will vary according to age but takes into account the higher cadmium intake on a bodyweight basis by infants and children. The PTWI has been set on the basis of a total intake of 1 µg/kg bw. per day for 50 years leading to levels in the renal cortex of 50 mg/kg which do not cause low-molecular-weight proteinuria.

The Committee has not received any data which would lead it to disagree with the evaluations established by JECFA for those two environmental contaminants.

Guidelines for Presentation of Data for Toxicological Evaluation of a Substance to be Used in Materials and Articles Intended to Come into Contact with Foodstuffs

(Version adopted officially by the Scientific Committee for Food on 18 May 1990)

Introduction

These guidelines are written for plastic materials and articles, but they are also largely applicable to any material in contact with foodstuffs for which a list of authorised substances (positive list) is provided. Food utensils and any surface intended to come into contact with foodstuffs are also covered in this document by the term "packaging materials".

Packaging materials can contain substances that are capable of migrating into the packaged food. These toxicological guidelines are designed to assess potential hazards to consumers resulting from oral exposure due to migration of packaging substances into food.

Substances persisting in the environment can have harmful effects on the environment and/or can accumulate in food chains. There is currently no requirement for supplying information on the persistence of a substance in the environment, or on its ecotoxicological impact, to the Scientific Committee for Food. This information may have to be suplied to the appropriate competent authority. The fate of substances in the finished material or article after it has been submitted to waste disposal treatment is also considered by other competent authorities.

The safety in use of a substance in packaging materials depends on many factors, for example :

A. the biological properties of the substance (see point 6);

B. the maximum quantity of the substance likely to be consumed per day, which depends on:

   i. the types of packaging materials which contain the substance;

   ii. the fraction of each packaging material which contains the substance and quantities of the substance incorporated;

iii. the length of contact of the foods with the materials, the unit weight of food in relation to the surface area of packaging and temperatures encountered while food is in contact with the material;

iv. the extent of migration of the substance or of its breakdown products into each type of food and its possible reactions with food components;

v. the types of food packaged;

vi. the proportion of each type of food which is packaged in each type of packaging material;

vii. the quantities of foods consumed which have been in contact with each of the packaging materials containing the substance;

C. the frequency with which food containing the substance or its breakdown products or its reaction products with food is consumed;

D. the period over which food containing the substance is consumed. This is related to the period over which the substance is actually used in the manufacture of packaging materials intended for food contact. Technological advances have produced increasingly sophisticated types of packaging materials and many substances have been used in packaging formulations for limited periods, to be superseded by others. Some substances however have been in use for more than 20 years.

Substances migrating into food are not necessarily identical with substances used in the production of the packaging. Therefore, in assessing the safety of packaging materials, it is the toxicity of the substance which migrates that has to be assessed, since it is only this substance to which the consumer of the food is exposed.

In order to assess any risks to public health from using a substance in the production of food packaging materials, it is necessary to determine the identity of the chemical or chemicals which actually migrate into food, the quantities (in average and in extreme cases) which migrate into the total daily diet, and the toxicological profile of each chemical.

These guidelines set out the minimum data required to achieve the above objectives when approval of a new substance is being sought.

Information to be supplied for the evaluation of a substance to be used in materials and articles in contact with food

Reports submitted must contain sufficient details for evaluation. They should be structured in the order given below under 1-6. Justification for any deviation from the following guidelines must be given.

Any reference to published information offered in support of an application should be accompanied by reprints or photocopies of such references.

A summary of data must also be prepared:

1. Identity of the substance

1.1 In the case of an individual, well-defined substance, give:

1.1.1 Chemical names (IUPAC and some synonyms such as common name, CAS name and trade name).

1.1.2 CAS number.

1.1.3 Molecular and structural formulae; molecular weight.

1.1.4 Degree of purity; methods for determination of purity; qualitative and quantitative data concerning impurities.

1.1.5 Spectroscopic and physico-chemical data; supply all other data which allow identification and characterisation of the substance, including physical state, melting point, boiling pint, decomposition temperature, flash point, vapour pressure and solubility in relevant solvents.

1.2 In the case of mixtures deal with each substance separately, in accordance with the sections 1.1.1 - 1.1.5 and give the proportions of the various substances in the mixture.

1.3 In the case of mixtures which cannot be completely defined, a description as complete as possible should be supplied, including :

1.3.1 The compounds or raw materials used in preparing the mixture;

1.3.2 The production process, production control and reproducibility of the process;

1.3.3 The method used to purify the product;

1.3.4 The substances formed during the process.

1.4 In the case of a polymer being used as an additive, give its structure, the starting substances (and relative amounts), the average and range of molecular weights.

If the molecular weight is not readily obtainable, furnish other characteristics of the polymer that are functions of the molecular weight such as intrinsic or relative viscosities or melt flow index. Give the concentration of residual monomers.

2. Chemical properties and stability

2.1 Stability of the substance in the finished product on exposure to factors such as e.g. light, air, ionising radiation, heat, water and oxidative treatments.

2.2 Information on any decomposition or transformation which the substance may undergo while the material or article is being manufactured; an indication of the decomposition or transformation products which may be formed in the finished material or article during production; the maximum temperature reached in the manufacturing process.

2.3 Information on possible chemical reactions of the migrating substance with food components.

3. Use

3.1 Technological function of the substance.

3.2 All types of material in which the substance is intended to be used.

3.3 Any particular use of the material (eg. microwave).

3.4 Maximum percentage in the formulation.

3.5 Maximum percentage which may remain in the material or article, when the amount given under 3.4 is reduced by chemical reactions and by processes such as washing, purification, evaporation, etc.

3.6 Mention any restrictions for use, e.g. type of foodstuffs, type of material, contact conditions, temperature, etc.

4. Information on authorisation given by countries and on evaluation by international organisations

• **State in which countries** and under what conditions the substance is authorised for use in contact with food. Include reference to the official publication concerning the authorisation.

• **State by which international organisations** evaluations have been made and enclose copies of relevant documents.

5. Migration data

Ideally, in order to permit estimation of the daily intake of the substance, data should be provided on the extent of migration of the substance, its breakdown and reaction products (specific migration) from each of its formulations into each of the food types packaged under all foreseeable conditions of storage and use. In practice, detection and analysis of low concentrations of substances and breakdown and reaction products migrating into food is often difficult. Thus the only way to determine potential migration into food may be to use food simulants.

When food simulants are used, the recommendations concerning the specific and overall migration established in EEC directives [1,2,3] or guidelines have to be followed. If the packaging material is used under conditions for which there are no specific indications in the EEC directives or guidelines (e.g. boiling bags, microwave applications, food irradiation), other testing conditions simulating actual use may be employed in consultation with the competent authorities.

If the substance is largely transformed during the processes and/or if potentially toxic reaction products are suspected, then data on the specific migration of the reaction products should be supplied.

Migration tests should be carried out with all the materials described in 3.2 (e.g. all types of plastic); in each instance with the maximum percentage of the substance defined in section 3.4 and the largest thickness intended to be used.

Details of migration tests must be reported, particularly the following :

5.1 Detailed composition of sample used, including initial concentration of any identified migrant, obtained by solvent extraction of the sample.

5.2 Food or food simulant(s) used.

5.3 Conditions of contact such as time, temperature, ratio surface/volume or weight of food or food simulant, type of migration cell used or any other parameter which can influence the level of migration.

5.4 Describe in detail the analytical method(s) and procedure(s) used for the quantitative determination of the substance(s) or its/their decomposition or transformation products. In cases where a specific migration limit is likely to be established, a method of analysis should be proposed and described **according to the EEC model** [4]. It should be a method which is suitable for food packaging control and which can be applied with consistent results by any properly equipped and trained laboratory personnel.

6. Toxicological data

6.1 The general requirements for toxicological studies which have to be supplied for substances in packaging materials are set out below.

- In carrying out toxicological tests, the aim should be to obtain the maximum amount of relevant information using a minimum number of animals [5].
- In deciding on the choice of studies, it should be recognised that not all chemicals used in the manufacture of a packaging material will migrate into food. Many will form a stable part of a polymer, some will migrate only in minute quantities, if at all, others will disappear during production, while yet others will decompose completely to yield either no or insignificant residues.
- While many substances migrate in the same chemical form in which they were incorporated into packaging materials, others will migrate partially or totally in another chemical form (see section 5). In such cases the toxicological requirements may also apply to transformation or reaction products.

6.2 The essential core set of tests which has to be carried out comprises :

- a 90-day oral study
- 3 mutagenicity studies :

  i. a test for gene-mutations in bacteria;

  ii. a test for chromosomal aberrations in cultured mammalian cells,

  iii. a test for gene-mutations in cultured mammalian cells; under special circumstances another validated eukaryotic test detecting gene-mutations may be acceptable;

- studies on absorption, distribution, metabolism and excretion;
- data on reproduction;
- data on teratogenicity;
- data on long-term toxicity/carcinogenicity.

These studies should be carried out according to **EEC Directives [6,7] and/or OECD guidelines, including "Good Laboratory Practice"** [8,9,10,11]. The test substances should be of the same specification as described in section 1.

If the abovementioned studies or prior knowledge indicate that relevant biological effects may occur, additional studies may be required.

At present no validated methods are available for studies in laboratory animals which would allow assessment of a substance's potential to cause intolerance and/or allergic reactions in susceptible individuals following oral exposure. However, studies on dermal or inhalation sensitization may give information relevant to possible hazards from occupational exposure and could be helpful in assessing consumer safety.

Observations in man as provided by health records of people employed in manufacture of the substance and, if relevant, of the polymer, would be regarded as useful ancillary information.

6.3 As a general principle, the greater the extent of migration into food, the more toxicological information will be required.

6.3.1 In cases where **migration is above 5 mg/kg of food/food simulant**, all the studies on the core list should be carried out. If any test is omitted this must be justified by providing appropriate reasons.

Under certain circumstances not all the core tests may be required, but at least the following should be carried out :

6.3.2 In cases where **migration is in the range of 0.05 - 5 mg/kg of food/food simulant:**

- demonstrate the **absence of potential for bioaccumulation in animals** (e.g. octanol/water partition coefficient);
- demonstrate the **absence of mutagenic potential** by the 3 mutagenicity tests listed above;
- supply a 90-day oral toxicity study.

6.3.3 In cases where **migration is lower than 0.05 mg/kg of food/food simulant:**

- demonstrate the **absence of mutagenic potential** by the 3 mutagenicity tests listed above;

6.3.4 As an alternative to determining the migration values mentioned in points 6.3.1, 6.3.2 and 6.3.3, it is possible to calculate the maximum level of migration by assuming that 100 % of the substance in question migrates from the packaging material into food/food simulants.

6.3.5 In some cases results of hydrolysis studies may justify a reduction in toxicological testing. This may arise when the chemical structure suggests ready hydrolysis into substances which are toxicologically acceptable (e.g. stearic acid ethyl ester, which may hydrolyse into a fatty acid and ethyl alcohol). Demonstration of hydrolysis may be carried out in foods or food simulants, representing the range of foods with which the substance may come into contact. Alternatively, or in cases where hydrolysis in food does not occur, hydrolysis can be evaluated in simulated saliva and/or gastrointestinal fluids.

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4) EEC document "Note for the guidance of the applicants " III/3568/89 Rev. 3 or updated version.

5) Council Directive 86/609/EEC of 24 November 1986 (O.J. N. L. 358 of 18.12.1986, p. 1).

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The Scientific Committee for Food was established by Commission Decision 74/234/EEC of 16 April 1974 (OJ L 136, 20.5.1974, page 1) to advise the Commission on any problem relating to the protection of the health and safety of persons arising from the consumption of food, and in particular the composition of food, processes which are liable to modify food, the use of food additives and other processing aids as well as the presence of contaminants.

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 deals with a second series of food additives of various technological functions (opinion expressed on 19 October 1990), nitrates and nitrites (opinion expressed on 19 October 1990), health aspects of the release of lead from capsules for wine (opinion expressed on 7 December 1989), toxicity of lead and cadmium in ceramics (opinion expressed on 7 December 1989), and guidelines for presentation of data for toxicological evaluation of a substance to be used in materials and articles intended to come into contact with foodstuffs (version adopted officially by the Scientific Committee for Food on 18 May 1990).