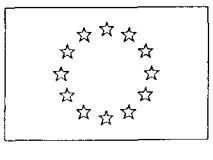
FOOD
SCIENCE AND TECHNIQUES

REPORTS OF THE SCIENTIFIC COMMITTEE FOR FOOD

(fortieth series)



EUROPEAN COMMISSION

European Commission

food science and techniques

Reports of the Scientific Committee for Food

(fortieth series)

REPORTS OF THE SCIENTIFIC COMMITTEE FOR FOOD ON:

Endocrine disruptors and food

OPINIONS OF THE SCIENTIFIC COMMITTEE FOR FOOD ON:

Additives in nutrient preparations for use in infant formulae, follow-on formulae and weaning foods

Opinion on Bisphenol A Diglycidyl Ether

The potential risk to human health arising from the transport in ships' tanks of oils and fats from substances proposed as acceptable previous cargoes

The microbiological safety of modified-atmosphere packaged (MAP) and controlled-atmosphere packaged (CAP) foods

Propane-1,2-diol

The assessment of novel foods:

Part ii: Recommendations concerning the scientific aspects of the presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients

Part iii: Recommendations concerning the scientific aspects of the preparation of the initial assessment reports on applications for placing on the market of novel foods and novel food ingredients

Directorate-General Industry
1997

published by the

European Commission
Directorate-General Industry

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Luxembourg : Office for Official Publications of the European Communities, 1997

ISBN.....

Printed in.....

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For their valuable and kind assistance to the following studies, the Scientific Committee for Food wishes to thank:

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P. ELIAS	UNIVERSITÄT HOHENHEIM (GERMANY)
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REPORT ON ENDOCRINE DISRUPTORS AND FOOD

(adopted on 7 June 1996)

Terms of reference

To advise the Commission on any areas of concern for health arising from recent research demonstrating that certain natural and man-made substances may have endocrine disruptor activity and may be present in food, and to propose a strategy for addressing them.

Background

1. A number of publications have appeared during the last 5 years concerning the prevalence of human and wildlife reproductive health problems, their possible association with exposure to environmental chemicals, along with *in vivo* and *in vitro* laboratory studies on environmental chemicals and endocrine disruptor activity (see references 1-5 for reviews). Whilst it has been known for many years that the human food and water supply may contain substances which have inherent hormonal activity, it was hitherto thought that the biological activity of these substances in humans at the levels present in food and water was probably negligible. However, the recent studies referred to above have prompted reassessment of whether such substances may have the potential to disrupt endocrine functions in man, particularly if exposure occurs during vulnerable periods of development.

2. The term "endocrine disruptor" has been usefully defined by an international workshop convened in 1995 by the US Environmental Protection Agency as:-

> *"An exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes."*[6]

This is a very broad definition and encompasses endocrine activity of any type (e.g. sex hormones, thyroid hormones, adrenal hormones, etc). A range of possible effects has been claimed for endocrine disruptors, including carcinogenesis, reproductive/developmental toxicity, immunotoxicity and neurotoxicity. However to date the focus of attention has been mainly on human and wildlife studies of sexual and reproductive function and a search for chemicals with oestrogenic, anti-oestrogenic, androgenic and anti-androgenic activity. This background paper is confined to a consideration of these latter areas of endocrine function.

3. The new aspects of the endocrine disruptor debate are not the well-described endocrine and reproductive toxicities which are seen when some man-made chemicals are given at high doses and which should be picked up in conventional toxicity studies, but whether adverse effects in humans might be triggered by:-

i) additive or synergistic action of chemicals, or bioaccumulation of persistent chemicals with weak endocrine disruptor activity,

ii) low doses of individual chemicals with potent but hitherto unrevealed endocrine disruptor activity,

iii) substantial exposure to natural oestrogens in the diet.

4. It is further assumed that the developing organism may be particularly sensitive to such effects. Thus, effects of existing chemicals may not be have been picked up by standard toxicity screening studies because they generally focus on single chemicals and/or do not study either endocrine activity or reproductive development and function in sufficient detail to reveal subtly-expressed effects.

5. The wildlife and human health effects that are causing concern have been extensively reviewed elsewhere[1-5] and it seems unecessary for the SCF to duplicate that effort. However, in order to orient Committee members who may be unfamiliar with the existing reviews, a brief summary of the key findings is given below. It is worth noting that the debate on endocrine disruptors is already moving at a fast pace as scientists worldwide reflect on the earlier papers and publish critiques of the data and the hypotheses on environmental causation. The pace is set to further accelerate as extensive research programmes get underway, funded by governments and industry in both Europe and North America.

Findings in wildlife and domestic animals

6. The following observations are among those cited as evidence of endocrine disruptor activity of natural and man-made environmental chemicals in domestic animals and wildlife.

i) Infertility, abortion, postnatal loss of offspring, reproductive tissue changes in cattle, sheep, pigs and poultry exposed to natural oestrogens present in pasture and feed.

ii) Pseudohermaphroditism or imposex (females developing male characteristics) in marine gastropods exposed to tributyltin from use of antifouling compounds on ships.

iii) Disruption of embryonic development *in ovo* of the reproductive system of alligators exposed to the pollutants dicofol and DDT and its metabolites in Lake Apopka, Florida, USA.

iv) Feminisation of gulls and terns exposed to organochlorines living along the Pacific Coast of the USA.

v) Hermaphroditism and vitellogenin secretion in male fish exposed to sewage effluent.

vi) Masculinisation of female fish and feminisation of male fish exposed to pulp mill effluent.

vii) Disturbances of endocrine homeostasis, development and reproductive function in fish and avian species living in and around the Great Lakes in North America.

Findings on human reproductive effects

7. The possible trends of concern in humans have been identified as:-

i) Increasing incidence of testicular cancer in young men.

ii) Decline in sperm count, sperm quality and semen volume.

iii) Increasing incidence of cryptorchidism (maldescended testes).

iv) Increasing incidence of hypospadias (a congenital defect in which the urethral opening on the penis is abnormally positioned).

v) Increasing incidence of breast cancer in men and women.

8. The evidence for an increasing incidence of testicular cancer in some geographical areas is strong, particularly in many (but not all) European countries, Australia, New Zealand and the USA. The evidence for a decline in sperm parameters is patchy, varies geographically even within single countries and has been subject to extensive critiques over methodology, selection of subjects and the appropriateness of the statistical meta-analysis which first drew attention to this issue.[7] The evidence for generalised increases in cryptorchidism and hypospadias is based on few studies and is equivocal. The increasing incidence of breast cancer in women in many countries is unequivocal, while limited evidence suggests there may be an increase in this rare condition in men.

The Sharpe-Skakkebaek hypothesis

9. The development of thinking in this area has been considerably influenced by the Sharpe-Skakkebaek hypothesis published in 1993.[8] They proposed that increases in reproductive tract abnormalities in the human male may be related to increased oestrogen exposure *in utero*. This suggestion stems from theoretical considerations that testicular cancer, cryptorchidism, hypospadias and low sperm counts all probably have their origin during fetal development, and the observation that similar abnormalities of the reproductive tract (though not testicular cancer) have been seen in the sons of women exposed to the powerful synthetic oestrogen, diethylstilboestrol (DES), during pregnancy.

10. The theory behind the hypothesis runs as follows. The number of Sertoli cells in the testis is known to determine the ultimate size of the testis in both rats and humans. Sperm production capacity is also dependent on the number of Sertoli cells since they can only support a fixed number of germ cells. Multiplication of Sertoli cells occurs in prenatal, neonatal and prepubertal life, starting from around day 19 of gestation in rats and from around week 7 of gestation in humans. Sertoli cells themselves multiply and produce oestrogen under the influence of follicle-stimulating hormone (FSH) from the pituitary, and oestrogen in turn is thought to exert a negative feedback on FSH secretion. FSH is also thought to regulate production of Mullerian inhibiting substance (MIS) which causes

regression of the Mullerian ducts in males. Persistence of the Mullerian ducts is associated with failure of testicular descent. Oestrogens may also control the numbers of Leydig cells in the fetal testis and it is these cells which secrete testosterone and influence male reproductive tract development. Exogenous oestrogens could therefore interfere with FSH and MIS secretion and thereby adversely affect Sertoli cells, germ cells and male reproductive tract development. MIS may also be responsible for control of multiplying germ cells during fetal life and its supression could allow development of abnormal germ cells which develop into testicular cancer in later life. Disorders of genital development are associated with gonadal malignancy and cryptorchidism is a risk-factor for testicular cancer, which implies a common aetiology.

11. The Sharpe-Skakkebaek hypothesis has proved an attractive one in that it proposes a unifying theory of causation and has biological plausibility. However, not all of the aspects of developemntal physiology mentioned above are clearly established and, at this stage, the proposal of a general increase in exposure of the human population to environmental oestrogens in recent years is entirely speculative.

Chemicals identified as potential endocrine disruptors

12. At the same time as the human and wildlife evidence was emerging, laboratory studies in the early 1990s were beginning to identify (at first serendipitously) oestrogenic activity in a number of synthetic chemicals when tested *in vitro*. Several assays have been utilised, including proliferation of oestrogen-sensitive human breast cancer cell lines, recombinant yeast cell lines encoding the human oestrogen receptor, and binding to the fish liver oestrogen receptor. Some of these assays are extremely sensitive. The "E-screen" for example, which uses MCF7 human breast cancer cells, can operate over a concentration range of 10-million fold and hence detect activity of compounds which are a million-fold less active, weight for weight, than the standard substance oestradiol-17ß. Similarly, the yeast cells used in the recombinant yeast assay contain around 10% oestrogen receptor by weight and so are extremely sensitive. It is probably this extraordinary sensitivity which has led to the discovery of weak oestrogenic activity in some chemicals which are without apparent effects in standard toxicity studies. It has been proposed that the potential for activity of weak oestrogens in humans may still be considerable because, unlike the natural hormones present in the body, they may not be bound to sex hormone binding proteins and thus will be present in the free, active form in the plasma. However, it is also necessary to be cautious when assuming that interaction with oestrogen receptors *in vitro* will correlate with oestrogenic activity *in vivo*, particularly in the context of exposure via the diet which

may contain not only oestrogen agonists and partial agonists, but also oestrogen antagonists.

13. A list of man-made and natural chemicals which have been cited in the published literature to have oestrogenic, anti-oestrogenic or anti-androgenic activity (mostly following *in vitro* assay only) is given in Annex 1. Whilst the chemicals listed may at first sight seem diverse, many have phenolic moieties, as has oestradiol-17ß, or may be metabolised to phenols, or contain a functional equivalent of a phenol, such as a polar function that can act as a hydrogen bond acceptor.[9] (Phenol itself is inactive.[10]) Structures which are a long way removed from oestradiol but nevertheless still exhibit oestrogenicity are characterised by usually being hydrophobic (e.g. chlorinated pesticides), and thus environmentally persistent, so that their inherent weak activity may be magnified by bioaccumulation.

14. In the case of naturally occurring chemicals such as the phyto-oestrogens, their inherent activity is weak but overall it may be greater than that of the man-made chemicals (other than those deliberately synthesised as oestrogenic drugs) because of the quantities present in food.[11] Soya for example contains a number of oestrogenic substances from the isoflavones group with individual activities ranging from 1/500 to 1/1000 of that of oestradiol-17ß.[12] However, *in vivo* they may act both as partial agonists and partial antagonists depending on the hormonal background of the organism. For example, soya protein (60g/day) in women has been shown to have sufficient oestrogenic activity to significantly prolong the length of the menstrual cycle, by suppressing the mid-cycle surges of FSH and LH.[13]

15. It should be noted that as far as natural toxicants and widespread environmental contaminants are concerned, case-by-case consideration of endocrine disruptor activity may be a trap for the unwary. In the context of dietary exposure it would be important to assess overall exposure to oestrogens and anti-oestrogens in the diet as a whole. Some attempts have been made already to address this complex issue of overall exposures and the likelihood of effects in man by utilising mass balance considerations of potency.[14] These suggest that, based on current data, there is little potential for man-made chemicals to cause an adverse endocrine-related response in humans. However, most scientists consider that resolution of the differences between this view and the counter environmental oestrogen hypothesis requires further, extensive research of both a fundamental and applied nature.

Strategy for the SCF

16. Against this background, the Committee agreed:-

i. Chemicals on which it has already given an opinion : The Committee should review such evidence as exists currently about chemicals on which it has already given an opinion, recognising that any new conclusions reached are likely to be interim pending the outcome of further research. This will mainly involve re-visiting a number of chemicals used in food contact materials, such as phthalates, bisphenol A and alkyl polyethoxylates. The need to review these comes not only from the work discussed above but also from recent information about unexpected levels of contamination of food with some of these chemicals, e.g. phthalates in infant formulae[15] and bisphenol A in canned vegetables.[16]

ii. Naturally occurring oestrogens : The Committee should review the topic of naturally occuring oestrogens, including phyto-oestrogens and oestrogenic mycotoxins. This area has not previously been addressed by the Committee but it would be prudent to do so for public health reasons.

iii. Contaminants : In the area of contaminants, prominent chemical groups with potential endocrine disruptor activity are the dioxins and the polychlorinated biphenyls. These have not yet been addressed by the SCF but they have been suggested as topics for future SCOOP activities. It was agreed that endocrine activity should be included in any future reviews of health effects of these contaminants.

ANNEX 1

Chemicals cited as oestrogenic or having other endocrine disrupting potential

Oestrogenic

5-Octylphenol
4-Nonylphenol
Alkylphenol diethoxylates
PCBs (some congeners)
p,p'-DDT
o,p'-DDT
o,p'-DDE
p,p'-DDE
Dieldrin
Lindane
Methoxychlor
Chlordecone
Toxaphene
Endosulphan
Coumestrol*
Genistein*
Daidzein*
Zearalenol*
Zearalenone*
Butylbenzylphthalate
Di-n-butylphthalate
tert-Butylhydroxyanisole (BHA)
Bisphenol A
Bisphenol A diglycidyl ether
4-sec-Butylphenol
4-tert-Butylphenol
4-tert-Pentylphenol
4-Isopentylphenol
4-Hydroxybiphenyl
4,4'-Dihydroxybiphenyl

Anti-oestrogens

Dioxins (some congeners)
PCBs (some congeners)
Indole-3-carbinol**

Anti-androgens

Vinclozolin
p,p'-DDE

Notes to table

* *Naturally occuring substances with oestrogenic or anti-oestrogenic activity, depending on the hormonal background of the organism.*

** *Naturally occuring anti-oestrogen.*

N.B. An attempt has been made to ensure tha above list is comprehensive but it may not include every chemical cited to date as an endocrine disruptor.

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OPINION ON ADDITIVES IN NUTRIENT PREPARATIONS FOR USE IN INFANT FORMULAE, FOLLOW-ON FORMULAE AND WEANING FOODS

(expressed on 7 June 1996)

1. TERMS OF REFERENCE

To advise on the safety of a series of additives in nutrient preparations for use in infant formulae, follow-on formulae and weaning foods.

2. BACKGROUND

In previous reports[1-3], the SCF has included a list of additives acceptable for use in nutrient preparations for infant formulae, follow-on formulae and weaning foods. These additives were **gelatine, gum arabic (acacia gum)** and **silicon dioxide** at a maximum level of 10g/kg in the nutrient preparation. The last report[3] also added that **mannitol** is acceptable as a diluent to a maximum dilution of 1:1000 in preparations of vitamin B_{12}. This list (with the exception of gelatine) is included in the European Parliament and Council Directive on Additives Other Than Colours and Sweeteners[4]. (Gelatine was excluded as it was considered an edible substance).

In December 1992, the SCF adopted an opinion on "Certain Additives For Use In Infant Formula, Follow-on Formula and Weaning Foods"[5]. This opinion covered a series of additives submitted by industry for consideration by the SCF since they had not been considered in the SCF's earlier reports[1-3]. The industry submission included new or amended uses of various additives in nutrient preparations intended for addition to foods specially prepared for infants and young children. In accordance with the general principles outlined in the opening section of its opinion, the Committee requested more information about the functions of and justification for the use of these additives before coming to a final conclusion. It also requested quantitative estimates of the levels of carry-over into the final food if these additives were used at the concentrations requested.

Industry has now submitted this information. This opinion considers the justifications for need provided (3.1) and the safety implications at the given levels of carry-over into the final infant formula (3.2), follow-on formula (3.3) or weaning food (3.4). Many of the additives requested for use in nutrient preparations have previously been considered by the SCF for direct use in foods specially prepared for infants and young children as vitamins, minerals or as technological additives. Within each section, the relevant earlier SCF

considerations for each additive are outlined in these three categories. A new use for mannitol in nutrient preparations are also considered.

3. EVALUATION

3.1 Functions and Justification for Use

The justification provided for the use of these additives in nutrient preparations is given in the table below.

JUSTIFICATION FOR USE OF CERTAIN ADDITIVES IN NUTRIENT PREPARATIONS

E304	Ascorbyl palmitate	Antioxidant for sensitive fat soluble nutrients.
E306-309	Tocopherols	As above.
E330-333	Citrates	Buffering agents for spray-drying. Antioxidants for fat soluble vitamins.
E341(iii)	Tricalcium phosphate	Carrier, anti-caking and stabilising agent.
E471	Mono-and diglycerides of fatty acids	Coating agent for B-vitamins. Emulsifier for vitamin E.
E414	Gum arabic	Replacement for gelatine coating for fat-soluble vitamins when for use in halal/kosher or hypoallergenic formulae.
E322	Lecithins	Emulsifier for stability of pro-vitamin A.
E412	Mannitol	Carrier for vitamins used in low amounts.

The technological need for several of these additives in foods specially prepared for infants and young children was considered in a report from the UK's Food Advisory Committee[6] and the need for all the additives for direct use in foods in general has been accepted since they are all listed in the Directive on Additives Other Than Colours and Sweeteners[4] (except mannitol which is a permitted sweetener). The justification for their use in nutrient

preparations is similar to that for food usage since they essentially perform the same function in the nutrient preparation.

The Committee accepts the justification for need where provided for the additives requested.

3.2 Acceptability of Specific Additives in Nutrient Preparations for use in Infant Formulae.

Additives which are also vitamins

"E304 Ascorbyl palmitate and E306-309 Tocopherols

Previous SCF Reports[1,2] and the Commission Directive on infant formulae and follow-on formulae[7] list ascorbyl palmitate (E304) and alpha tocopherol (E307) as acceptable nutritional substances to be used as sources of Vitamins C and E respectively. In addition, all the tocopherols are listed in Annex VI of the Directive on Additives Other Than Colours and Sweeteners[4] as acceptable technological additives in infant formulae at up to 10 mg/l. *The Committee recommends that the use of ascorbyl palmitate and the tocopherols in nutrient preparations for infant formulae is acceptable if the total level of the additives in the formula is less than 1.5mg/100kcal."*

Additives containing minerals

Additives containing sodium (E331 sodium citrate and E554 sodium aluminium silicate)

Only a very small amount of additional sodium (0.5 µg and 0.8 µg/100 kJ) would result from the carry-over levels of sodium citrate and sodium aluminium silicate respectively. This compares with the range set for sodium in infant formulae of 5 - 14 mg/100 kJ[1,2,7]. Sodium citrate (but not sodium aluminium silicate) is listed as an acceptable dietetic additive to provide these recommended levels of sodium. *The Committee recommends that the use of sodium citrate and sodium aluminium silicate in nutrient preparations for infant formulae is acceptable with regard to the sodium content at carry-over levels of 0.1 mg/kg provided the total level of sodium does not exceed the maximum levels recommended by the SCF in its previous reports.*

Additives containing potassium (E332 potassium citrate)

Only a very small amount of additional potassium (0.8 µg/100 kJ) would result from the carry-over levels of potassium citrate. This compares with the range set for potassium in infant formulae of 15 - 35 mg/100 kJ[1,2,7]. Potassium citrate is listed as an acceptable

dietetic additives to provide these recommended levels of potassium. *The Committee recommends that, with regard to the potassium content, the use of potassium citrate in nutrient preparations for infant formulae is acceptable at carry-over levels of 15μg/100kcal provided the total level of potassium does not exceed the maximum levels in infant formulae recommended by the SCF in its previous reports.*

Additives containing calcium or phosphorus (E333 calcium citrate and E341(iii) tricalcium phosphate)

Carry-over of calcium citrate at 0.1 mg/l would lead to a maximum Ca content of 0.8 μ g/100 kJ. This compares with the minimum requirement for calcium in infant formula of 12 mg/100 kJ[1,2,7]. Carry-over of tricalcium phosphate ($Ca_3(PO_4)_2$) was not given precisely ("within the range for calcium and phosphorus") but the ratio on a mg basis of calcium to phosphorus in tricalcium phosphate (1.9:1) is within the acceptable range for infant formulae (1.2:1 - 2:1). Both calcium citrate and tricalcium phosphate are listed as acceptable dietetic additives to provide calcium and tricalcium phosphate is acceptable to provide phosphorus in infant formulae[1,2,7]. The Committee is aware that there may be variable levels of aluminium as a contaminant in tricalcium phosphate. *The Committee recommends, bearing in mind the necessity to meet the legal requirements for calcium, phosphorus and the ratio between them, that the use of tricalcium phosphate and calcium citrate is acceptable. A limit for aluminium in the specification for tricalcium phosphate should be considered.*

Additives in nutrient preparations previously considered as direct additives in infant formulae, follow-on formulae or weaning foods

E471 Mono- and diglycerides of fatty acids

E471 is listed as acceptable up to a maximum of 4g/l in infant formulae[1,4]. *The Committee recommends that the use of mono- and diglycerides of fatty acids in nutrient preparations for use in infant formulae is acceptable within the direct additive limit (4g/l).*

E330-333 Citric acid and sodium, potassium and calcium salts

Sodium, potassium and calcium citrates have already been discussed in the context of the sodium, potassium and calcium content. This paragraph addresses the acceptability of the citrate anion.

In a previous report[1], the Committee considered citric acid as an acceptable technological additive for acidified milks although no maximum level was given. The Directive on

Additives Other Than Colours and Sweeteners[4] lists the *quantum satis* use of citric acid in infant formulae as acceptable. Weak organic acids are reabsorbed more readily by tubular cells in young infants, due to the low pH of the urine[8]. However, the extra citrate reabsorbed as a result of carry-over levels of 0.1 mg/kg is unlikely to be significant. The UK Committee on Medical Aspects of Food and Nutrition Policy considered the acid-base balance of infant formulae and concluded there was no need for specific recommendations other than that the pH of a new infant formula should not be too dissimilar from that of well established infant formulae[9]. *The Committee recommends that the carry-over of citric acid or its salts is acceptable in infant formulae at a carry-over level of 0.1mg/kg.*

E322 Lecithins

In an earlier report[1], the Committee considered lecithins as acceptable technological additives at levels up to 5 g/l. However, the Directive on Additives Other Than Colours and Sweeteners[4] lists the maximum level as 1g/l. This reduction in the maximum level was agreed during the negotiations on the draft Directive in response to a report[6] which recommended that the maximum level of lecithins in infant formulae should be restricted to that of human milk (1g/l). This recommendation was based on studies which claimed neuro-behavioural effects in the offspring of rats fed high doses of lecithin. Although these studies were of poor quality, the report noted that large increases in plasma choline could affect neurotransmission in the brain and that particular caution was needed in the infant since the brain was still actively developing.

The Committee's earlier report[1] did consider choline and concluded that, although choline was not a vitamin, considerable amounts were needed for neonatal membrane synthesis. Choline was listed as an acceptable dietetic additive but supplementation was not compulsory and no minimum or maximum levels were set.

In animals and humans, administration of choline or lecithin increases blood choline levels and, in animals, brain choline levels and acetyl choline synthesis are also increased[10,11]. (No studies examining whether brain choline or acetyl choline was increased in human infants in response to high blood levels of choline were available to the Committee). High brain uptake of choline has been shown in young animals[11] and the background blood level of choline is higher in neonates than in adults[12]. No studies were found with human infants indicating whether excessive levels of choline had any functional consequences. However, the Committee noted that the long-chain polyunsaturated fatty acid (LCP) composition of the diet can affect red blood cell and cerebral cortex lipid composition in infants and that red blood cell LCP content is correlated with visual acuity in pre-term infants[13,14]. Thus, the Committee considered there was a theoretical possibility that high

levels of lecithin in formulas could have functional consequences and wished to examine the issue further.

The Committee considers that the issue of lecithins and choline in infant formulae should be considered further. However, in the context of carry-over levels of only 0.5 mg/kg, the use of lecithins in nutrient preparations for infant formulae is acceptable and not likely to be of concern.

E414 Gum arabic/acacia gum

Although permitted in weaning foods, gum arabic is not on the list of acceptable direct technological additives in the SCF Report on infant formulae[1]. Furthermore, the report stated that no thickening agents other than pre-cooked or gelatinized starches should be used. A similar statement from the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)[15] was based on general concerns over (i) lack of need, (ii) the possibility of persorption and (iii) insufficient toxicological data. In the case of gum arabic however, the Committee considered the need as a coating agent was justified, persorption was unlikely as gum arabic swells in water to form a gel and the toxicological studies available on gum arabic were extensive. Although there were no multigeneration studies including exposure prior to weaning, the toxicological data did not raise any issues likely to be of particular concern for infants and young children. *The Committee concludes that, at the low level of carry-over of 10 mg/kg, the use of gum arabic as a coating agent for vitamin preparations for use in infant formulae is acceptable. It should be emphasised that this acceptance does not apply to use as a thickening agent in much larger quantities in infant formulae, an issue that would need to be considered separately.*

Additives in nutrient preparations <u>not</u> previously considered as direct additives in infant formulae, follow-on formulae or weaning foods

E421 Mannitol

Mannitol is already listed as an acceptable carrier for vitamin B_{12}[1,4]. Industry have now requested permission to use mannitol as a carrier for Biotin. The level of carry-over in the final food in both cases is 3 mg/kg. Mannitol was considered acceptable as a sweetener[16] for general food use but it was recommended that polyols should not be used in foods specially prepared for infants and young children due to their laxative effects. However, these effects have only been reported with mannitol at doses over 10 g/day. *The Committee recommends that since there is no risk of laxative effects at 3 mg/kg, the use of mannitol as a carrier for biotin in infant formulae is acceptable.*

3.3 Acceptability of Specific Additives in Nutrient Preparations for use in Follow-on Formulae

Additives which are also vitamins

E304 Ascorbyl palmitate and E306-309 Tocopherols

The evaluations referred to when considering these additives in infant formulae also apply to follow-on formulae.

Additives containing minerals

Additives containing sodium (E331 sodium citrate and E554 sodium aluminium silicate)

For follow-on formulae, there is no maximum limit set for sodium in the composition Directive[7] since it is stated that mineral levels must be "at least equal to" those in cow's milk in relation to the protein content rather than "in the range of" as stated in the SCF Reports[1,2]. Only a very small amount of additional sodium (0.5 µg and 0.8 µg/100 kJ) would result from the carry-over levels of sodium citrate and sodium aluminium silicate respectively. This compares with the amount of sodium in follow-on formulae equivalent to that in cow's milk of 7.5 - 15 mg/100 kJ. *The Committee recommends that the use of sodium citrate and sodium aluminium silicate in nutrient preparations for follow-on formulae is acceptable with regard to the sodium content at carry-over levels of 0.1 mg/kg provided the total level of sodium does not exceed the maximum levels in follow-on formulae recommended by the SCF in its previous reports.*

Additives containing potassium (E332 potassium citrate)

For follow-on formulae, there is no maximum limit set for potassium in the Directive[7] since it is stated that mineral levels must be "at least equal to" those in cow's milk in relation to the protein content rather than "in the range of" as stated in the SCF Reports[1,2]. Only a very small amount of additional potassium (0.8 µg/100 kJ) would result from the carry-over levels of potassium citrate. This compares with the amount of potassium in follow-on formulae equivalent to that in cow's milk of 21.5 - 43 mg/100 kJ. *The Committee recommends that, with regard to the potassium content, the use of potassium citrate in nutrient preparations for follow-on formulae is acceptable at carry-over levels of 15 µg/100kcal provided the total level of potassium does not exceed the maximum levels in follow-on formulae recommended by the SCF in its previous reports.*

Additives containing calcium or phosphorus (E333 calcium citrate and E341(iii) tricalcium phosphate)

Carry-over of calcium citrate at 0.1 mg/l would lead to a maximum Ca content of 0.8 μg/100 kJ. This compares with the range of calcium in follow-on formulae which would be equivalent to that in cow's milk in relation to the protein content (17.5 - 35 mg/100 kJ)[1,2,7]. Carry-over of tricalcium phosphate ($Ca_3(PO_4)_2$) was not given precisely ("within the range for calcium and phosphorus") but the ratio on a mg basis of calcium to phosphorus in tricalcium phosphate (1.9:1) is within the acceptable range for follow-on formulae (< 2:1) (1,2,7). Both calcium citrate and tricalcium phosphate are listed as acceptable dietetic additives to provide calcium and tricalcium phosphate is acceptable to provide phosphorus in follow-on formulae[1,2,7]. *The Committee recommends, bearing in mind the necessity to meet the legal requirements for calcium, phosphorus and the ratio between them, that the use of tricalcium phosphate and calcium citrate is acceptable.*

Additives in nutrient preparations previously considered as direct additives in infant formulae, follow-on formulae or weaning foods

E471 Mono- and diglycerides of fatty acids

The evaluations referred to when considering these additives in infant formulae also apply to follow-on formulae.

E330-333 Citric acid and sodium, potassium and calcium salts

The evaluations referred to when considering these additives in infant formulae also apply to follow-on formulae.

E322 Lecithins

As in infant formulae, lecithins were considered acceptable in follow-on formulae at levels up to 5 g/l[1] and this level was reduced to 1 g/l in the Directive on Additives Other Than Colours and Sweeteners[4]. The theoretical concerns about high lecithin intakes would still apply at weaning age since rapid brain development continues throughout the first year and follow-on formulae are likely to be used at the early stages of weaning. However, as with infant formulae, carry-over levels of 0.5 mg/kg are unlikely to be of concern.

E414 Gum arabic/acacia gum

Gum arabic is not listed as an acceptable additive in follow-on formulae but other thickening agents are listed[1,4]. The evaluation in the context of infant formulae, also applies to the carry-over of gum arabic in follow-on formulae.

Additives in nutrient preparations not previously considered as direct additives in infant formulae, follow-on formulae or weaning foods

E421 Mannitol

The evaluations referred to when considering mannitol in infant formulae also apply to follow-on formulae.

3.4 Acceptability of Specific Additives in Nutrient Preparations for use in Weaning Foods

Additives which are also vitamins

E304 Ascorbyl palmitate and E306-309 Tocopherols

Ascorbyl palmitate (E304) and alpha tocopherol (E307) are listed as acceptable dietetic additives to be used as sources of vitamins C and E in weaning foods[3,17]. Ascorbyl palmitate and all the tocopherols are listed as acceptable technological additives in weaning foods[3,4]. The level specified is 100 mg/kg in fat-containing cereals, biscuits and babyfoods. Thus, the carry-over of ascorbyl palmitate and the tocopherols from the use of vitamin preparations in these foods could be regarded as acceptable within this limit. The Committee was informed that carry-over levels in the final food would be "according to SCF recommendations for vitamins C and E". However, there is no maximum level for vitamin C and vitamin E which would apply in fat-free products[3,4,17].

The Committee recommends that the use of ascorbyl palmitate and the tocopherols in nutrient preparations for fat-containing weaning foods is acceptable within the direct additive limit of 100 mg/kg. However, industry should be asked whether vitamin preparations containing ascorbyl palmitate or the tocopherols are used in fat-free weaning foods and, if so, what the carry-over level would be.

Additives which contain minerals

Additives containing sodium (E331 sodium citrate)

Maximum levels for sodium have been set in various types of weaning foods[3,17]. Also, for cereal-based foods, products based on fruit, desserts or puddings, it is stated that sodium salts should only be added for technological purposes[17]. For sodium citrate, it is unclear whether there is a technological need for the sodium salt rather than another citrate salt, although the need has been justified for citrates in general.
Most of the maximum levels for sodium (except savoury baby foods) have only been set on an energy basis but no standard energy content is set. It is therefore difficult to compare the limit for sodium with the carry-over of sodium from the additives. However, the carry-over contribution to the maximum sodium content in savoury baby foods (200 mg/100g)is extremely small (0.01 mg/100g) and sodium citrate is already listed as acceptable in weaning foods as a direct additive[3,4]. *In view of the low levels, the Committee is not concerned about the carry-over of sodium from the use of sodium citrate.*

Additives containing potassium (E332 potassium citrate)

In contrast to sodium, there are no requirements set for potassium in weaning foods[3,17] although potassium citrate is listed as an approved nutritional substance. Potassium citrate is listed as an acceptable direct additive[3,4]. *The Committee recommends that, from the point of view of the potassium content, the use of potassium citrate in nutrient preparations for weaning foods is acceptable at carry-over levels of 0.1 15 µg/100kcal.*

Additives containing calcium or phosphorus (E333 calcium citrate and E341(iii) tricalcium phosphate)

In weaning foods, only a minimum calcium content is specified in "cereals with an added high protein food" and "rusks and biscuits" and there are no suggested minimum or maximum limits for phosphates in any weaning foods. Tricalcium phosphate and calcium citrate are listed as approved nutritional substances[3,17]. No calcium to phosphorus ratio is specified[3] although the recommendation for follow-on formulae of < 2:1 on a mg basis applies to infants over 4 months[1,2]. The Committee has recommended a population reference intake (PRI) for age 6 - 11 months of 400 mg/day for calcium and 300 mg/day for phosphorus[19]. This is equivalent to a ratio of 1.3:1 on a mg basis. This report also notes that, for infants, the molar ratio should be between 0.9 and 1.7:1 (1.2 to 2.2:1 on a mg basis). Calcium citrate (*quantum satis* for pH adjustment) and calcium phosphates

(1 g/kg expressed as P_2O_5 in combination with sodium and potassium phosphates in cereals) are both acceptable as direct additives in weaning foods[3,17].

Surveys of the diet of infants aged 6 - 12 months from various European countries found calcium intakes in the range 606-863 mg/day[18,20,21]. Phosphorus intakes were less frequently measured but ranged from 650-770 mg/day[18,21]. The calcium to phosphorus ratio varied from 0.97:1 to 1.12:1 on a mg basis. This is lower than the recommended range for infants. However, the original research examining the effects of calcium to phosphorus ratios on plasma calcium levels was performed with 6-day old infants[22]. This research was prompted by concern that hypocalcaemia and tetany seen in neonates occurred more often in artificially-fed infants[9]. Adults can tolerate wider variations in calcium to phosphorus ratios[19] and older infants are better able to excrete excess solutes than younger infants.

The total phosphorus intake for a 6-month old infant (650 mg/day[21]; 87 mg/kg bw/day) exceeds the TDI of 70 mg/kg bw/day for the sum of phosphates (expressed as phosphorus) naturally present in food and derived from additives. This TDI was set by JECFA[23] and endorsed by the SCF[24] for diets adequate in calcium. It was acknowledged that the TDI could be higher if intakes of calcium were higher. Cow's milk and foods prepared for the whole family contribute more to the total phosphorus intake in 6 - 12 month old infants than commercial weaning foods[18] and the contribution of the carry-over from tricalcium phosphate to phosphate intake from commercial weaning foods is likely to be very small. (It is not possible to calculate the carry-over because this was specified as "according to SCF recommendations for calcium". These recommendations are only given on an energy basis and do not cover all categories of weaning foods).

The Committee recommends that the use of tricalcium phosphate is acceptable within the direct additive limit of 1g/kg in simple cereals but, for other types of weaning foods, information on carry-over levels is needed from industry. A limit for aluminium in the specification for tricalcium phosphate should also be considered. The carry-over of calcium citrate at 0.1 mg/kg in weaning foods is acceptable.

Additives in nutrient preparations previously considered as direct additives in infant formulae and follow-on formulae or weaning foods

E471 Mono- and diglycerides of fatty acids

Mono- and diglycerides of fatty acids are acceptable as direct additives at up to 5g/kg (singly or in combination with E472a,b or c) in biscuits and rusks, cereal-based foods or baby foods[3,4]. *The Committee recommends that the use of mono- and diglycerides of fatty*

acids in nutrient preparations for use in weaning foods is acceptable within the direct additive limit of 5g/kg.

E330-333 Citric acid and sodium, potassium and calcium salts

Citric acid and its sodium, potassium and calcium salts are listed as acceptable technological additives *(quantum satis* for pH adjustment only)[4]. *The Committee recommends that the carry-over of citric acid or its salts is acceptable in weaning foods at a carry-over level of 0.1mg/kg.*

E322 Lecithins

Lecithins are listed as permitted direct additives at 10g/kg in biscuits and rusks, cereal-based foods and baby foods[4]. Although the theoretical concerns about high lecithin intakes would still apply at weaning age since rapid brain development continues throughout the first year, the contribution from lecithin as an additive will be a lower proportion of total intake as infants consume a more diverse diet. The contribution from carry-over levels of lecithin of 0.5 mg/kg will be even less significant. *The Committee considers that, in the context of carry-over levels of only 0.5 mg/kg, the use of lecithins in nutrient preparations for weaning foods is acceptable and not likely to be of concern.*

E414 Gum arabic/acacia gum

Gum arabic is listed as acceptable for use as a direct additive in weaning foods at up to 10g/kg and in gluten-free cereal-based foods at up to 20g/kg[3,4]. *The Committee recommends that the use of gum arabic as a coating agent for vitamin preparations for use in weaning foods is acceptable within the direct additive limits.*

Additives in nutrient preparations <u>not</u> previously considered as direct additives in infant formulae, follow-on formulae or weaning foods

E421 Mannitol

The evaluations referred to when considering mannitol in infant formulae also apply to weaning foods.

4. GENERAL CONSIDERATIONS

The Committee was asked to comment on some general points arising from the evaluations of additives in nutrient preparations for use in foods specially prepared for infants and young children.

Should limits be set in the nutrient preparation or the final food?

From the toxicological point of view, the key issue is whether the infant's overall intake of the carry-over additive is a cause for concern. Thus, the levels in the final foods and the consumption of those foods are the important pieces of information rather than the original source of the carry-over additive. Issues such as whether, for enforcement, analysis of nutrient preparations would be easier than analysis of lower quantities in the final food are outside the remit of the Committee. *The Committee recommends that, as is usual, its opinions should be expressed on the basis of levels in final foods. The question of whether limits should be set in nutrient preparations themselves is a matter for the Commission and Member States.*

Could the SCF state that all nutrients permitted in infant foods may be used as technological additives as far as overall consumption is not affected?

The SCF Report on infant formulae[1] already states (Annex 4) that for special vitamin formulations any edible substances and additives recommended in the rest of the report may be used. This principle works reasonably well for infant formulae and, to a certain extent, follow-on formulae because appropriate ranges for vitamins and minerals are set out in detail. However, in some cases there are only minimum requirements. The situation is more complex when considering carry-over into weaning foods since there are fewer precise recommendations and such recommendations as there are may only apply to certain categories of weaning foods. *The Committee was reluctant to make any general statement which might allow increased use of additives in infant formulae, follow-on formulae and weaning foods without further scrutiny.*

Could the SCF state that all additives permitted in certain categories of infant food may also be used in nutrient preparations to be used in this category.

Levels of use for direct additives can be orders of magnitude higher than carry-over levels but any general statement should not be taken as an encouragement of high carry-over levels. *The Committee recommends that all additives permitted in certain categories of*

infant food may also be used in nutrient preparations to be used in this category provided the carry-over levels are sufficiently low to raise no new health questions.

Could the SCF state that foods and food ingredients may be used for nutrient preparations as far as they are permitted for infant foods.

There are only a few recommendations as to what specific foods or food ingredients should be used in infant foods. As mentioned above, it has already been stated[1] that for special vitamin formulations any edible substances and additives recommended in the rest of the report may be used for infant formulae[1,3]. *The Committee reiterates its earlier statement that any edible substances recommended in infant formulae, follow-on formulae or weaning foods may be used in nutrient preparations for the appropriate category of infant food. In addition, the final formula including carry-over of the food or food ingredient should still comply with the overall compositional requirements (protein, lipid, carbohydrate content, amino acid composition etc.).*

5. CONCLUSIONS

The Committee's recommendations on specific additives are summarised below.

Infant formulae

Carry-over additive		*Opinion*
E304	Ascorbyl palmitate	Acceptable within limit for E304
E306-9	Tocopherols	Acceptable within limit for E306-309
E330	Citric acid*	Acceptable within carry-over of up to 0.1 mg/kg
E331	Sodium citrate*	Acceptable within limit for Na and carry-over of up to 0.1 mg/kg
E332	Potassium citrate*	Acceptable within limit for K and carry-over of up to 0.1 mg/kg
E333	Calcium citrate*	Acceptable within limit for Ca and Ca/P ratio and carry-over of up to 0.1 mg/kg
E341iii	Tricalcium phosphate	Acceptable within limit for Ca and Ca/P ratio. A limit for aluminium in the specification should be considered
E471	Mono- and diglycerides	Acceptable within limit for E471
E322	Lecithins*	Acceptable within carry-over of up to 0.5 mg/kg

E414	Gum arabic	Acceptable within carry-over of up to 10 mg/kg
E421	Mannitol	Acceptable within carry-over of up to 3 mg/kg

* Citric acid and lecithins are also permitted direct additives but are either permitted without specific limits (e.g. citric acid) or the limit is being reconsidered (e.g. lecithins). NB. The acceptability as a carry-over additive of E414 should not be taken to mean this additive is acceptable for use directly as a thickening agent, an issue which would need to be considered separately.

Follow-on formulae

Carry-over additive		*Opinion*
E304	Ascorbyl palmitate	Acceptable within limit for E304
E306-9	Tocopherols	Acceptable within limit for E306-309
E330	Citric acid*	Acceptable within carry-over of up to 0.1 mg/kg
E331	Sodium citrate*	Acceptable within limit for Na (in SCF Report) and carry-over of up to 0.1 mg/kg
E332	Potassium citrate*	Acceptable within limit for K (in SCF Report) and carry-over of up to 0.1 mg/kg
E333	Calcium citrate*	Acceptable within limit for Ca and Ca/P ratio and carry-over of up to 0.1 mg/kg
E341iii	Tricalcium phosphate	Acceptable within limit for Ca and Ca/P ratio. A limit for aluminium in the specification should be considered.
E471	Mono- and diglycerides	Acceptable within limit for E471
E322	Lecithins*	Acceptable within carry-over of up to 0.5 mg/kg
E414	Gum arabic	Acceptable within carry-over of up to 10 mg/kg
E421	Mannitol	Acceptable within carry-over of up to 3 mg/kg

* Citric acid and lecithins are also permitted direct additives but are either permitted without specific limits (e.g. citric acid) or the limit is being reconsidered (e.g. lecithins).

Weaning Foods

Carry-over additive		*Opinion*
E304	Ascorbyl palmitate	Acceptable within limit for E304 in fat-containing cereals, biscuits and babyfoods. Information needed on carry-over levels needed in weaning

		foods other than fat-containing cereals, biscuits and babyfoods
E306-9	Tocopherols	Acceptable within limit for E306-309 in fat-containing cereals, biscuits and babyfoods. Information needed on carry-over levels needed in weaning foods other than fat-containing cereals, biscuits and babyfoods
E330	Citric acid*	Acceptable within carry-over of up to 0.1 mg/kg
E331	Sodium citrate	Acceptable within carry-over of up to 0.1 mg/kg and within limit for Na where specified
E332	Potassium citrate*	Acceptable within carry-over of up to 0.1 mg/kg
E333	Calcium citrate*	Acceptable within carry-over of up to 0.1 mg/kg
E341iii	Tricalcium phosphate	Acceptable within limit for E341iii in simple cereals. A limit for aluminium in the specification should be considered. Information needed on carry-over levels required in other types of weaning foods.
E471	Mono- and diglycerides	Acceptable within limit for E471
E322	Lecithins*	Acceptable within carry-over of up to 0.5 mg/kg
E414	Gum arabic	Acceptable within limit for E414
E421	Mannitol	Acceptable within carry-over of up to 3 mg/kg

* Citric acid, the citrates and lecithins are also permitted direct additives but are either permitted only for specific purposes (e.g. citric acid and citrates for pH adjustment) or the limit is being reconsidered (e.g. lecithins).

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OPINION ON
BISPHENOL A DIGLYCIDYL ETHER
(Expressed on 7 June 1996)

Terms of reference

To re-evaluate the substance from a toxicological point of view in the light of the new documentation available.

Background

Bisphenol A diglycidyl ether (BADGE, PM/REF. No. 13510) is used in the production of plastic food contact materials. It was evaluated as a monomer by the Committee in 1987 and classified into list 4A (list 4A consists of substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or in food simulants is not detectable by an agreed sensitive method) (1). The compound was subsequently included in the Council Directive on monomers, 90/128/EEC, with the requirement that it should not be detectable in food at the detection limit of 20 ppb (2).

Recent analyses by official laboratories in several countries have revealed high migration of BADGE, particularly in Switzerland and also in Germany in certain food products. The levels found by the Swiss authorities ranged from 0.4 - 56 ppm in the oil of certain canned fish products and as a consequence the sale of these products was banned. The analytical findings were confirmed by further independent analyses (3). Following these events the Commission requested the Committee to re-examine urgently the available data on BADGE.

The Commission had previously received a request from industry to re-evaluate this monomer as part of its programme of preparing directives to harmonise legislation in Member States of the EU on food contact materials (4).

Discussion

The Committee was provided with extensive documentation most of which was already available to it, when it prepared the evaluation of BADGE in 1987. Additional studies submitted were a one-generation reproduction study dated 1989 (5), a two-generation reproduction study completed in 1996 (6) and two teratology studies dated 1988 (7, 8). The Committee was also informed that BADGE is used both as a processing aid (i.e. an

additive) in PVC based coatings and as an intermediate (i.e. a monomer) in the manufacture of epoxy resins. This former use implies that some of the BADGE would not participate in the polymerisation reactions forming the coating but would remain unreacted and thus be liable to migration into any foodstuff in contact with such coatings, particularly fatty foods.

In the opinion of the Committee, the compound is mutagenic in several *in vitro* assays using different endpoints. The available *in vivo* mutagenicity studies provided negative results. However, these studies are inadequate to demonstrate the lack of activity *in vivo* because
i) limitations in or poor validation of the testing procedures which used somatic cells, or
ii) some of the tests were carried out on germ cells, which are inappropriate targets for excluding a hazard to somatic cells. Although a DNA-binding study using the dermal route produced DNA-adducts of unidentified structure deriving from a possible theoretical metabolite of BADGE, available metabolism studies have shown that BADGE is rapidly absorbed after oral administration and essentially detoxified by epoxide hydratase. In order to exclude an in vivo mutagenic activity of the compound, which is expected in any case to be weak if at all, a test for chromosomal damage in rodent bone marrow such as a micronucleus test or a metaphase analysis should be carried out. If the result of this test is negative, a test for DNA damage/repair in another target tissue, e.g. unscheduled DNA synthesis in rat liver, is needed.

No adequate oral subchronic and chronic studies are available. However, several carcinogenicity studies using dermal application were available for evaluation. They show that only BADGE containing substantial amounts of epichlorohydrin produced weak tumorigenic effects (skin and systemic lesions) but there was no evidence that BADGE itself was carcinogenic when applied directly to the skin. It is known that up to 20% can be absorbed after application to the skin.

The reproduction and teratology studies showed that BADGE did not possess any potential for toxicity to reproduction and was not teratogenic. The two-generation reproduction study showed some shortcomings with low fertility of the animals used including controls. However the earlier one-generation reproduction study showed no evidence of any interference with the fertility of the test animals.

Conclusion

In the absence of an adequate oral chronic/carcinogenicity study, or a 90-day study, and pending clarification of the potential for *in vivo* mutagenic activity, the Committee is unable to set a TDI for BADGE. Bearing in mind that for substances used in plastic food contact materials in general, a restriction of migration to 5 mg/kg food can be set, provided genotoxicity and bioaccumulation are absent and an adequate oral 90 day study is available,

the Committee proposes a temporary restriction of migration to the lower figure of 1 mg/kg food, taking into account the negative 28-day oral study (with a NOAEL of 1000 mg/kg b.w. but only using small numbers of animals), and a clear no-effect level of 20 mg/kg b.w. from the reproduction and teratology studies (liver weight being the affected parameter).

The Committee also considered the issue of possible oestrogenicity of BADGE which has been tested *in vitro* in human breast cancer cell line MCF7. The effect on cell proliferation was questionable (between 5-7 orders of magnitude lower than that of 17 β-oestradiol). Moreover, BADGE does not bind to oestrogen receptors (9). In view of the *in vitro* results and the fact that no effect were seen on fertility in the two reproduction studies, the Committee is satisfied that no further data on reproduction are needed.

In conclusion the substance is moved from list 4A into list 7 (list 7 consists of substances for which some toxicological data exist, but for which an ADI or TDI could not be established) and the following data should be supplied:

a) a test for chromosomal damage in rodent bone marrow such as a micronucleus test or a metaphase analysis. If the result of this test is negative, a test for DNA damage/repair in another target tissue, e.g; unscheduled DNA synthesis in rat liver (deadline: 1 year);
b) an adequate oral 90-day study (deadline: 2 years).

In the mean time the upper limit of 1 mg/kg of food as a temporary restriction for specific migration of BADGE and its hydrolysis products should be enforced.

References

1. SCF Reports seventeenth series (1987) CEC, Luxembourg.

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OPINION ON THE POTENTIAL RISK TO HUMAN HEALTH ARISING FROM THE TRANSPORT IN SHIPS' TANKS OF OILS AND FATS FROM SUBSTANCES PROPOSED AS ACCEPTABLE PREVIOUS CARGOES

(expressed on 20 September 1996)

Terms of Reference

The Committee is asked to assess the risk to human health arising from potential contamination of oils and fats shipped in tanks which may have been used to transport the substances as given in the Annex to a derogating directive 96/3/EC(1) from certain provisions of the hygiene of foodstuffs directive 93/43/EEC(2). In so doing the Committee is specifically asked to examine the substances

- on the current list (Annex to the Commission Directive 96/3)
- that may be proposed for addition to the list

In assessing the risk associated with contamination of oils and fats by the above substances, the Committee is asked to take account of information to be provided by industry concerning:

- the likelihood and potential level of contamination in the light of information concerning, where appropriate, cleaning procedures, dilution and limits of detection of analytical methods, and,
- the additional processing of the oils and fats.

Background

Chapter IV of the Annex to the directive on the Hygiene of Foodstuffs 93/43/EEC requires bulk liquid, granulate and powdered foods to be transported in receptacles and/or containers/tankers reserved for foodstuffs only.

The Commission and Member States recognised that the application of this requirement to the bulk transport of liquid oils and fats in ships would be impractical and could lead to unreasonable restrictions to world trade in these commodities. The bulk transport of oils and fats by sea is currently conducted under the internationally recognised rules of the Federation of Oil Seeds and Fats Associations (FOSFA) which have reduced contamination occurrences to nearly zero. These rules do not require dedicated transport but allow for oils and fats to be

transported in bulk tanks which have previously been used to transport substances from a positive list.

The Commission had sought and acquired the approval of a directive introducing a derogation for the bulk transport of liquid oils and fats in ships subject to certain safeguards. These reflected those in the FOSFA rules including the application of an acceptable previous cargoes list given in the Annex to the derogating directive 96/3/EC.

Article 4 of the derogating directive requires that it: *"shall be reviewed where one or more Member States, or the Commission consider that amendments are necessary in order to take account of scientific or technical developments. In any case the Annex shall be reviewed within one year of the adoption of this Directive"*

In drawing up the derogation the Commission had taken account of the Codex code on oils and fats which includes conditions for shipping these commodities by referring to the FOSFA rules. The views of the SCF on the substances in the Annex to the derogating directive are the subject of this opinion.

Review of the Annex to the Commission Directive

Taking into account the terms of reference and its mandate, the Committee has focused its attention on the evaluation of the toxicological properties of the substances on the list of acceptable previous cargoes for transport of bulk liquid oils and fats, without considering other aspects, such as, ecotoxicological characteristics, microbial status or nutritional relevance. Neither were the specifications of the transported oils and fats nor the purity of the previous cargo taken into account.

On this basis, the Committee considered that the acceptability of the substances in the list of acceptable previous cargoes be based on the following criteria:

- no toxicological concerns, particularly with regard to their genotoxic and carcinogenic potential, for which a threshold is difficult to establish;

- efficacy of procedures used to clean ships' tanks between cargoes;

- dilution factor in relation to the potential amount of residue of the previous cargo and any impurity which the previous cargo might have contained and the quantity of oil or fat transported;

- subsequent application of refining processes and solubility relevant to the occurrence of possible contaminating residues;.

- availability of analytical methods to verify the presence of trace amounts of residues or the absence of contamination of oils and fats.

In considering the acceptability of the substances as previous cargoes the Committee noted that the Hygiene of Foodstuffs Directive 93/43/EEC requires all foodstuffs to be protected from the risk of contamination. In addition, it noted that in relation to the transport of foodstuffs where the conveyance and/or container has been used for the transport of anything other than foodstuffs, or for transporting different foodstuffs, Directive 93/43/EEC requires effective cleaning to be undertaken between loads to avoid the risk of contamination. The Committee also noted that the derogating directive 96/3/EC, allowing for the transport by sea of oils and fats in tanks not solely reserved for foodstuffs, includes a requirement for the captain of the vessel to keep accurate documented evidence relating to the three previous cargoes and the effectiveness of the cleaning process between these cargoes.

With regard to the toxicological evaluation, the Committee has taken into account, where applicable, its previous opinions, as well as those of JECFA or other recognised bodies and the fact that a threshold for genotoxic or carcinogenic potential is difficult to establish. This approach was possible for most of the substances included in Annex 1.

Some substances were considered acceptable because they are food (acids oils and fatty acid distillates; animal, marine and vegetable and hydrogenated oils) or food component (Enanthyl alcohol, Lauryl myristyl alcohol; Cetyl stearyl alcohol).

For other substances acceptance was more problematic for several reasons.

These were:

-iso-Decanol, }
} no toxicological data (SCF List 8
-iso-Nonanol, } of Food Contact Materials)
} mixtures of isomers of uncertain composition
-iso-Octanol, }

-Montan wax: regarded as temporarily acceptable by the Committee as a food additive, highly insoluble.

-Paraffin wax: insufficient data to establish the safety of all types of mineral hydrocarbon waxes(SCF)

-White Mineral Oils: certain types regarded as temporarily acceptable by the Committee pending submission of a 2 year chronic-carcinogenicity study.

-Methyl tertiary butyl ether (MTB): acceptable pending evaluation by the SCF of a long term NTP study.

For these substances the Committee considers that priority should be given to their reassessment within the terms of the review clause in the Directive. These substances have however been provisionally accepted after considering mainly their unlikely genotoxic potential, their easy removal by tank cleaning procedures, and the very low residues expected as a result of these factors and their likely dilution.

Finally, ten substances (see annex 2 and 3) were considered not acceptable for reasons such as inadequate toxicological and /or technical data (Methyl laurate, Methyl palmitate, Methyl stearate, Methyl oleate, nonane, and 2,3 - Butanediol) or because of some concern over their genotoxic and carcinogenic potential (iso-Butanol, Cyclohexanol and Cyclohexanone).

Conclusions

The Committee has examined the list of acceptable previous cargoes contained in the annex to Commission Directive 96/3/EC granting a derogation for the transport of bulk liquid oils and fats by sea from the provisions of Chapter IV, paragraph 2, first indent of the Annex to Directive 93/43/EEC on the hygiene of foodstuffs. Taking into account the criteria listed in its mandate, the Committee recommends to the Commission that the list of substances contained in Annex 1 of this opinion may be considered to be acceptable as previous cargoes to be carried in ships' tanks which are subsequently to be used for the transport of edible oils and/or fats.

However these substances are only considered as acceptable as long as the provisions of the Hygiene of Foodstuffs Directive 93/43/EEC apply, including the conditions in the derogating directive 96/3/EC, particularly those relating to the cleaning and condition of tanks and the availability of analytical methods. The Committee recognises the importance of ensuring that cleaning agents do not cause contamination of oils and fats and has received assurances that this aspect is covered not only in the Hygiene of Foodstuffs Directive 93/43/EEC, the derogating Directive 96/3/EC but also in the international standards for the bulk transport of oils and fats by sea.
The Committee would wish to reassess those substances in Annex 1 whose acceptance is provisional as new scientific and/or technical data becomes available within the terms of the review clause in Directive 96/3.

References

1. Commission directive 96/3EC granting a derogation from certain provisions of Council Directive 93/43/EEC on the hygiene of foodstuffs as regards the transport of bulk liquid oils and fats by sea. O. J. N°. L21, 27.01.96, p. 42

2. Council Directive 93/43/EEC on the Hygiene of Foodstuffs June 1993; O.J. N°.175, 9.7.1993, p. 25

ANNEX 1

List of Acceptable Previous Cargoes

Substance	CAS N°	Remarks
Acetic Acid (ethanoic acid; vinegar acid; methane carboxylic acid)	64-19-7	E260 Food Additive. ADI not specified (SCF. 25th report)
Acetic anhydride (ethanoic anhydride)	108-24-7	During tank washing or on contact with water would be converted to Acetic acid.(*q.v.*)
Acetone - (dimethylketone; 2-propanone)	67-64-1	Acceptable as extraction solvent for food. (SCF. 29th report)
Acid Oils and Fatty Acid Distillates - from vegetable oils and fats and/or mixtures thereof and animal and marine fats and oils		Food.
Ammonium Hydroxide - (ammonium hydrate; ammonia solution; aqua ammonia)	1336-21-6	E527 Food Additive. ADI not specified. (SCF. 25th report)
Ammonium polyphosphate	10124-31-9	Toxicologically acceptable as a previous cargo in view of the Maximum Tolerable Daily Intake of 70mg/kg/BW for phosphate expressed as P. (SCF 25th report)
Animal, Marine and Vegetable and Hydrogenated Oils and Fats (other than cashew shell nut and tall oil)		Food.
Beeswax (white and yellow)	8006-40-4 8012-89-3	E901 Food Additive Acceptable for use as as a glazing agent for food. (SCF 26th report)
Benzyl alcohol - (Pharmaceutical and reagent grades only)	100-51-6	Group ADI 0 -5 mg/kg/BW. JECFA 1996. Report 46. Acceptable as extraction solvent for food. (SCF 11th report)

Substance	CAS N°	Remarks
Butyl Acetates - **n-Butyl acetate**	123-86-4	**n-Butyl acetate** **Temporary ADI 0 - 6 mg/kg/BW.** **Temporarily acceptable as an extraction solvent for food.** **(SCF 29th report)**
sec-butyl acetate	105-46-4	**sec-butyl acetate** **Limited toxicological data but no indication of a hazard.** **Easily removed by tank cleaning.**
tert-butyl acetate	540-88-5	**tert-butyl acetate** **Limited toxicological data but no indication of a hazard.** **Easily removed by tank cleaning.**
Calcium chloride solution (is acceptable as a previous cargo only where the immediate previous cargo to it is on this list and is not similarly restricted.)	10043-52-4	**E509** **Food Additive** **ADI not specified** **(SCF 25th report)**
Calcium lignosulphonate	8061-52-7	**Likely to be toxicologically inert. Easily removed by tank cleaning.** **Acceptable as an animal feedstuff.** **(Directive 70/524/EEC. O.J. L.270., 14. 12 .70)**
Candelilla wax	8006-44-8	**E902.** **Food Additive.** **Temporarily acceptable as a glazing agent for food.** **(SCF 26th report).**
Carnauba wax - (Brazil wax)	8015-86-9	**E903.** **Food Additive.** **Temporarily acceptable as a glazing agent for food.** **(SCF 26th and 36th report)**
Cyclohexane - (hexamethylene; hexanaphthene; hexahydrobenzene)	110-82-7	**Acceptable by SCF as an extraction solvent for flavourings.** **(SCF 97th plenary)**
Epoxidised soyabean oil (with a maximum 8% oxirane oxygen content)	8013-07-8	**Temporary TDI of 1 mg/kg BW. (SCF/ FCM Working Group 44th Meeting)**
Ethanol - (ethyl alcohol;)	64-17-5	**Acceptable as extraction and carrier solvent for food.** **(SCF 29th report)**
Ethyl acetate - (acetic ether; acetic ester; vinegar naphtha)	141-78-6	**Acceptable as extraction solvent for food** **(SCF 29th report)**

Substance	CAS N°	Remarks
2-Ethylhexanol - (2-ethylhexyl alcohol)	104-76-7	**ADI. 0.5mg/kgBW. Acceptable as a flavouring in food. (JECFA 1993 41st report)**
Fatty acids:		**Components of food, miscellaneous additives (SCF 25th report)**
Butyric Acid - (n-Butyric Acid; Butanoic Acid; Ethyl Acetic Acid; Propyl Formic Acid)	107-92-6	**List 0.(SCF 17th report)**
Valeric Acid - (n-Pentanoic Acid; Valerianic Acid)	109-52-4	**List 0.(SCF 30th report)**
Caproic Acid - (n-Hexanoic Acid)	142-62-1	**List 3.(SCF 33rd report)**
Heptoic Acid - (n-Heptanoic Acid)	111-14-8	**List 3.(SCF 33rd report)**
Caprylic Acid - (n-Octanoic Acid)	124-07-2	**List 3.(SCF 33rd report)**
Pelargonic Acid - (n-Nonanoic Acid)	112-05-0	**List 8.(SCF 30th report)**
Capric Acid - (n-Decanoic Acid)	334-48-5	**List 3.(SCF 33rd report)**
Lauric Acid - (n-Dodecanoic Acid)	143-07-7	**List 0.(SCF 33rd report)**
Lauroleic Acid - (Dodecenoic Acid)	4998-71-4	**Food**
Myristic Acid - (n-Tetradecanoic Acid)	544-63-8	**List 1. ADI not specified(SCF 33rd rep.)**
Myristoleic Acid - (n-Tetradecenoic Acid)	544-64-9	**List 8.(SCF 30th report)**
Palmitic Acid - (n-Hexadecanoic Acid)	57-10-3	**List 7.ADI not specified (SCF 33rd rep.)**
Palmitoleic Acid - (cis-9-Hexadecenoic Acid)	373-49-9	**List 0.(SCF 33rd report)**
Stearic Acid - (n-Octadecanoic Acid)	57-11-4	**List 1. ADI = NS(SCF 33rd report)**
Ricinoleic Acid - (cis 12-Hydroxy Octadec-9 Enoic Acid; Castor oil acid)	141-22-0	**List 2. TDI = 0.7 mg/kg/BW.(SCF 33rd report)**
Oleic Acid - (n-Octadecenoic Acid)	112-80-1	**List 1.(SCF 33rd report)**
Linoleic Acid - (9,12 - Octadecadienoic Acid)	60-33-3	**List 0.(SCF 33rd report)**
Linolenic Acid - (9,12,15 - Octadecatrienoic acid)	28290-79-1	**List 0.(SCF 33rd report)**
	463-40-1	
Arachidic Acid - (Eicosanoic Acid)	506-30-9	**List 0.(SCF 33rd report)**
Behenic Acid - (Docosanoic Acid)	112-85-6	**List 0.(SCF 33rd report)**
Erucic Acid - (Cis 13-Docosenoic Acid)	112-86-7	**List 3.SCF 33 rd Report)**

Substance	CAS N°	Remarks
Fatty alcohols		**Food**
Butyl alcohol - (1-Butanol; Butyric alcohol)	71-36-3 111-27-3	**List 3.(SCF 33rd report)** **List 3.(SCF 30th report)**
Caproyl alcohol - (1-Hexanol; hexyl alcohol)	111-70-6	**Component of food.**
Enanthyl alcohol - (1-Heptanol; Heptyl alcohol)	111-87-5	**List 3.(SCF 33rd report)**
Capryl alcohol - (1 n-Octanol)	143-08-8	**List 3.(SCF 30th report)**
Nonyl alcohol - (1-Nonanol; Pelargonic alcohol; octyl carbinol)	112-30-1	**List 3.(SCF 33rd report)**
Decyl alcohol - (1-Decanol)	112-53-8	**List 3.(SCF 33rd report)**
Lauryl alcohol - (n-Dodecanol; Dodecyl alcohol)	112-70-9	**List 3.(SCF 33rd report)**
Tridecyl alcohol - (1-Tridecanol)	112-72-1	**List 3.(SCF 33rd report)**
Myristyl alcohol - (1-Tetradecanol; Tetradecanol)	36653-82-4	**List 3.(SCF 33rd report)**
Cetyl alcohol - (Alcohol C-16; 1-Hexadecanol; Cetylic Alcohol; Palmityl alcohol; n-primary Hexadecyl alcohol)	112-92-5	**List 3.(SCF 33rd report)**
Stearyl alcohol - (1-Octadecanol)	143-28-2	**List 3.(SCF 33rd report)**
Oleyl alcohol - (Octadecenol)		**Component of food**
Lauryl Myristyl alcohol - (C12-C14 blend)		**Component of food**
Cetyl Stearyl alcohol - (C16-C18 blend)		
Fatty acid esters - (any ester produced by the combination of any of the above listed fatty acids with any of the above listed fatty alcohols. Examples of these are butyl myristrate, oleyl palmitate and cetyl stearate.)		**Unlikely to cause health problems if present in trace amounts. Processing would reduce possible contamination to low levels . Easily removed by tank cleaning.**
Formic acid - (Methanoic Acid; Hydrogen Carboxylic Acid)	64-18-6	**Group ADI 0 - 3 mg/kg/BW for formic acid and ethyl formate.** **(JECFA 1973. 17th Report)**
Glycerol - (Glycerine; Glycerin)	56-81-5	**E422.** **Food Additive and component of food.** **ADI not specified** **(SCF 11th Report)**

Substance	CAS N°	Remarks
Glycols -		
Butanediol		
1-3 butanediol -(1.3-butylene glycol)	107-88-0	List 1. ADI 4 mg/kg/BW (SCF 17th Report) (JECFA 23rd)
1.4-butanediol -(1.4-butylene glycol)	110-63-4	List 8. (SCF 17th report) Some toxicological data on short term effects and developmental toxicity. Technical data relating to the substances cleanability from tanks considered as highly soluble in water. From its chemical structure unlikely to be genotoxic.
Polypropylene glycol - (molecular weight greater than 400)	25322-69-4	TDI - 1.5 mg/kg BW. List 2. (SCF 97th meeting 1-2/06/95)
Propylene Glycol - (1.2 propylene glycol; propan-1, 2-diol; 1.2-dihydroxypropane; Monopropylene glycol (MPG); Methyl glycol)	57-55-6	Food Additive ADI 25 mg/kg BW. (SCF 103 rd Plenary. September 1996)
n-Heptane -	142-82-5	Acceptable as an extraction solvent for food. (JECFA 1970. 14th report)
Hexane (technical grades for oils seed extraction)	110-54-3 64742-49-0	Acceptable as an extraction solvent for food. (SCF 35th report)
iso-Butyl acetate	110-19-0	Generally used as a flavouring in food on FEMA and GRAS lists.
iso-Decanol (Isodecyl alcohol)	25339-17-7	Easily removed by the oil refining process. Provisionally accepted.
iso-Nonanol (Isononyl alcohol)	27458-94-2	Easily removed by the oil refining process. Provisionally accepted.

Substance	CAS N°	Remarks
iso-Octanol (Isooctyl alcohol)	26952-21-6	Easily removed by the oil refining process. Provisionally accepted.
iso-Propanol - (Isopropyl alcohol; IPA)	67-63-0	Acceptable as an extraction solvent for food provided that residues are very low. Readily removed by tank cleaning and easily removed by the oil refining process.
Limonene - (Dipentene)	138-86-3	Generally used as flavouring for food. ADI not specified (JECFA. 1993 41st report) (USA Reg. 182.60)
Magnesium chloride solution	7786-30-3	E511 Food Additive. ADI not specified. (SCF 25th report)
Methanol - (Methyl alcohol)	67-56-1	ADI not set. Acceptable as extraction solvent for food. (SCF 29th report) In the 29 th report the SCF gave its opinion that methanol may be present up to levels of 5 - 10 mg/kg food when used as an extraction solvent. Although there was insufficient data to establish an ADI, the Committee considered the residues arising from its use to be minimal, constituting no safety problem, and therefore set no ADI. The substance is readily removed by tank cleaning, and is easly removed by the oil refining process.
Methyl ethyl ketone - (2-Butanone)	78-93-3	Acceptable as extraction solvent for food. (SCF 29 th report)
Methyl isobutyl ketone - (4-methyl-2-pentanone)	108-10-1	List 3 Food contact material component. Restriction = 5 mg/kg/food SCF 17/09/93
Methyl tertiary butyl ether - (MTBE)	1634-04-4	Provisionally accepted pending evaluation by SCF of studies concerning its use as an extraction solvent for food.

Substance	CAS N°	Remarks
Molasses	57-50-1	Acceptable residue from sugar processing.
Montan wax	8002-53-7	E912 Food Additive Temporarily acceptable as glazing agent for food. (SCF 26th report) Highly insoluble. Provisionally accepted.
Paraffin Wax (Petroleum Wax)	8002-74-2 & 63231-60-7	Existing SCF opinion on mineral hydrocarbons - waxes states that there are insufficient data to establish the safety of paraffin waxes. (SCF 37th report) However given the nature of the toxicity of paraffin waxes it would not be expected that very low residues would give rise to problems. The normal cleaning process involving heating of the tank should ensure the removal of paraffin waxes to acceptable residual levels. Provisionally accepted.
n-Pentane -	109-66-0	List 3 (SCF 33rd report). Will be removed by the refining process.
Phosphoric acid - (Ortho Phosphoric Acid)	7664-38-2	E338. Food Additive. Maximum Tolerable Daily Intake is 70mg/kg BW for phosphate expressed as P. (SCF 25th report).
Potable water is acceptable as a previous cargo only where the immediate previous cargo to it is on this list, and is not similarly restricted.		
Potassium hydroxide (caustic potash) is acceptable as a previous cargo only where the immediate previous cargo to it is on this list and is not similarly restricted.	1310-58-3	E525 Food Additive. ADI not specified (SCF 25th report)
Propane-1-ol (Propyl alcohol;1-propanol)	71-23-8	Acceptable as an extraction solvent for foods. (SCF 29th report)

Substance	CAS N°	Remarks
n-Propyl acetate	**109-60-4**	**Generally used as a flavouring in food on FEMA and GRAS lists.**
Propylene tetramer	**6842-15-5**	**Some toxicological data available. It is not of structural concern. Subject to the examination of ongoing genotoxicity studies this substance is acceptable as a previous cargo. Low residue levels expected as easily removed by tank cleaning and easily removed by the oil during refining.**
Silicon dioxide(microsilica)	**7631-86-9**	**E551** **Food Additive** **ADI not specified** **(SCF 25th report)**
Sodium hydroxide (Caustic soda, lye) **is acceptable as a previous cargo only where the immediate previous cargo to it is on this list and is not similarly restricted.**	**1310-73-2**	**E524.** **Food Additive.** **ADI not specified.** **(SCF 25th report)**
Sodium silicate (Water glass)	**1344-09-8**	**Food Additive** **Group ADI not specified for silicates and silica** **(SCF 25th report)**
Sorbitol - (D-Sorbitol; Hexahydric alcohol; D-Sorbite)	**50-70-4**	**E420** **Food Additive** **ADI not specified** **(SCF 21st report)**
Sulphuric acid	**7664-93-9**	**E513;** **Food Additive.** **ADI not specified.** **(SCF 25th report)**
Urea ammonia nitrate solution - (UAN)	**Blend of 57-13-6 (urea) & 6484-52-2 (*Ammonium* nitrate)**	**Toxicologically acceptable as a previous cargo as very low residual levels expected.**

Substance	CAS N°	Remarks
White Mineral Oil	8042-47-5	**White paraffinic mineral oils derived from petroleum based hydrocarbon feedstocks and complying with the specification defined (viscosity not less than 8.5 centiStokes at 100°C, carbon number not less than 25 at the 5 % boiling point; average molecular weight not less than 480) were assigned a temporary ADI of 0 - 4 mg/kg/BW. pending the submission within four years of the results of a two - year chronic toxicity/carcinogenicity feeding study in rats incorporating a 1 year reversal phase. These oils encompass those known commercially as P70(H) and P100(H). There are insufficient data to establish the safety in the use of other mineral oils. (SCF 37th report) However given the nature of the toxicity of other mineral oils it would not be expected that very low residues would give rise to problems. The normal cleaning process involving heating of the tank should ensure the removal of white mineral oils to acceptable residual levels. Provisionally accepted**
Wine lees - (vinasses, vinaccia, argol, vini, argil arcilla, weinstein, crude cream of tartare, crude potassium bitartrate)	868-14-4	**Potassium tartrate E336 Food Additive. ADI 30mg/kg/Body Weight (SCF 25th report)**

Annex 2

Substances submitted for assessment by the SCF but considered as not acceptable at present as suitable substances for Immediate Previous Cargoes to oils and fats for human consumption.

Substance	Cas N°	Remarks
Cyclohexanol (hexahydrophenol)	108-93-0	NOT ACCEPTABLE See Annex 3.
Cyclohexanone	108-94-168	NOT ACCEPTABLE See Annex 3.
Fatty acid - Methyl Esters - Methyl laurate - (Methyl dodecanoate) Methyl palmitate - (Methyl hexadecanoate) Methyl stearate - (Methyl octadecanoate) Methyl oleate - (Methyl octadecenoate)	 111-82-0 112-39-0 112-61-8 112-62-9	NOT ACCEPTABLE Inadequate toxicological or technical data available. No data presented to the SCF concerning the ease of cleaning from tanks or the ease of removal during the refining process.
2.3-butanediol -(2.3-butylene glycol; 2.3 dihydroxybutane; pseudobutylene glycol; sym-dimethylethylene glycol	513-85-9	NOT ACCEPTABLE No toxicological data presented to the SCF. Limited technical data on ease of cleaning from the tank or removal by the oil refining process.
1.3-Propylene Glycol - (Trimethylene glycol; 1.3-propanediol)	504-63-2	NOT ACCEPTABLE Inadequate toxicological data presented to the SCF on a substance which is structurally of concern
iso-Butanol - (2-methyl-1-propanol;)	78-83-1	NOT ACCEPTABLE Limited toxicological data indicates a suspicion of carcinogenic concerns.
Nonane	111-84-2	NOT ACCEPTABLE Inadequate toxicological or technical data available. No data presented to the SCF concerning the ease of cleaning from tanks or the ease of removal during the refining process.

Annex 3

Cyclohexanol and cyclohexanone

Cyclohexanol

Cyclohexanol is currently accepted as a previous cargo in trade conducted under the internationally recognised FOSFA rules.

The SCF has evaluated cyclohexanol in conjunction with cyclohexanone because of structural similarity and metabolic interconversion between cyclohexanol and cylohexanone in vivo. There are no carcinogenicity data for cyclohexanol and limited mutagenicity data are equivocal with respect to clastogenicity.

Cyclohexanone

Cyclohexanone has been requested for addition to the list. 2-year carcinogenicity studies in rats and mice produced equivocal results, suggestive of a marginal effect in neoplasms. Data on genotoxicity were also equivocal indicating possible clastogenic effect.

The SCF consider that at this point in time there are inadequate data to fully evaluate these two substances but there are indications for concern regarding genotoxicity and carcinogenicity. For those reasons, the Committee is unable to endorse their inclusion in the list of acceptable previous cargoes.

THE MICROBIOLOGICAL SAFETY OF MODIFIED-ATMOSPHERE PACKAGED (MAP) AND CONTROLLED-ATMOSPHERE PACKAGED (CAP) FOODS

(expressed on 20 September 1996)

Terms of reference

The Committee is asked whether, in the light of the latest developments in science, it sees any microbiological hazards for human health, resulting from the current use of controlled or modified atmosphere as a method of preservation.

1. Background

Directive 94/54/EEC provides for the labelling of foodstuffs and requests the indication on the label that the food is packaged under special storage conditions. Increased consumer demand for fresh products and the strong tendency to centralized packaging have resulted in the rapid development of MAP and CAP foods over the past decade. A considerable research effort in MAP and CAP technology (packaging films, machinery, etc.) has supported this success. Further research on some items concerning their microbiological safety may still be needed and, more crucial, consumers should be made aware of microbiological hazards of the various types of MAP and CAP foods by means of practical recommendations.

2. Technological aspects of the application of controlled and modified atmospheres in food preservation

The change of the atmosphere surrounding a food during storage is referred to as application of controlled atmosphere (CA) or modified atmosphere (MA). The differentiation between CA and MA relates to adjusting well defined partial pressures for the respective gases in CA, whereas in MA less defined conditions prevail. In food preservation the changes in the composition of gases concern the content of O_2, N_2 and CO_2 relative to air. The Committee concludes that it does not see specific microbiological hazards for human health by the current use of a controlled or modified atmosphere.A prerequisite condition is that the principles of HACCP are observed.

CA or MA are applied to various types of foods such as meat, fish, fruits, vegetables, baked foods, pasta and convenience products. The composition of the gases in the atmosphere has to take into consideration the nature of the food. For example, a pure N_2 atmosphere is recommended for storage of cereals. Mixtures of CO_2 (>20%), O_2 and N_2 are used for meat, poultry and fish, the mixtures of the same gases with a CO_2 content of 5-10% are applied for fruits and vegetables.

These atmospheres extend the shelf-life of the food by preventing losses in quality due to spoilage of chemical, biochemical or microbial origin during storage. Closely related to these effects of CA and MA are vacuum packaging and the use of hyperbaric or hypobaric atmospheres, as they share as common principle a high content of CO_2. In all cases, the effect on the prolongation of shelf-life of the treated food depends on the concentration of this gaseous compound, and further on the storage temperature, the type and physiological status of the microflora and the composition of the food.

For inhibition of microbial growth CO_2 concentrations greater than 5% are required. Concentrations of CO_2 below 5% may stimulate the growth of certain groups of microorganisms. Over a CO_2 concentration range of 5-50% usually a linear dependence of the inhibitory effect on the CO_2 concentration can be observed, often resulting in a 50% inhibition of the growth of the sensitive flora at a 10% CO_2 concentration. At high concentrations (60-100%) , main applications of CO_2 are with hard cheeses, bakery products and oily fish *(1)*.

The various groups of microorganisms exhibit a characteristic response to increased CO_2 concentration. They may die out, their growth may be inhibited or they may not be affected. However, a sufficiently high inhibitory effect of growth is generally observed for the main spoilage flora prevalent in food of animal origin such as meat and meat products. This flora is mainly composed of psychrotrophic bacteria, e.g. *Pseudomonas* spp., *Acinetobacter* spp., *Moraxella* spp., etc. Fermenting microorganisms such as lactic acid bacteria are only poorly affected, develop to the prevalent flora and may finally limit the shelf-life. Thus, CA and MA exert a more selective effect on the spoilage flora and, to some extent, on food pathogens (*vide infra*). In general, CA and MA act synergistically with the effect of cold storage. Their effects relate to an extension of the lag phase of microorganisms and to a reduction of their growth rate. To make use of the important former effect, food to be CA- or MA-packaged has to be of high microbial quality, i.e. having a low bacterial count. When foodstuffs in which the microflora is already in the exponential growth phase are CA- or MA-packaged, no protective effect from CA or MA is observed. In addition, as CA and MA have a selective effect on microorganisms, the growth of certain foodborne pathogens cannot be excluded and, therefore, the well established effect of low temperatures on their growth has to be an integral part of the MAP and CAP foods concept. Thus, the temperature should be kept as low as in cold storage and the effect of CA and MA has to be considered as an additionally acting principle. Finally, effects of the food matrix on the growth of microorganisms have to be taken into consideration with regard to e.g. water activity, pH, compositions and implicit factors etc.

3. Behaviour of pathogens in MAP and CAP foods

In comparison to air packaging, it is estimated that under refrigerated storage modified atmospheres extend shelf-life of pork from 4 to 9 days, of beef from 4 to 12 days, of chicken from 6 to 18 days, of cooked meats from 7 to 28 days and of fish from 2 to 10 days (*1*). Prolongation of MAP foods shelf-life is achieved by inhibiting the spoilage organisms usually present and capable of growth in non-MAP foods, in which they are responsible for deleterious effects on organoleptic quality. However, under extended shelf-life and temperature abuse conditions, and depending on the bacterial strain and on the type of food, some pathogens may grow on certain MAP-foods reaching populations and producing amounts of toxins dangerous for the consumer. Growth of pathogens in MAP foods with moderate to high levels of CO_2 may be possible or even stimulated (*2*).

The great hazard related to MAP foods is the possibility that dangerously high levels of pathogens and of their toxins may be reached in unspoiled MAP-food before the expiration date under temperature-time abuse conditions, if spoilage organisms were inhibited by MA. Anaerobic pathogens such as the nonproteolytic psychrotrophic type E strains of *Clostridium botulinum* have been the major concern associated with MAP foods for the last two decades. More recently, psychrotrophic pathogens such as *Listeria monocytogens, Aeromonas hydrophila* and *Yersinia enterocolitica* have become new matters of concern for the safety aspects of MAP foods. Microbial risks due to the growth of the above mentioned and other pathogens on the main groups of MAP and CAP food commodities have been reviewed and discussed.

3.1. Fish and fish products

C. botulinum type E strains are the microorganisms of greatest concern associated with MAP fish products, mainly with those eaten without further cooking such as smoked salmon and cooked peeled shrimp. *C. botulinum* type E is a common natural seafood contaminant. An incidence of 14% was reported in freshly eviscerated whitefish chub from the Great Lakes, and incidence increased up to 20% after brining (*2*). Estimated MPN of *C. botulinum* was 0.09-2.4/g in red snapper and 0.03-1.2/g in salmon (*4*).

A temperature below 3°C is recommended for fish products to prevent growth of *C. botulinum* (*2*), as non-proteolytic *C. botulinum* type B, E and F are capable of growth at temperatures as low as 3.3°C. Botulinal toxins are heat -labile. However, spores of *C. Botulinum* are heat resistant and can survive smoking. As the number of competing microorganisms is reduced by this process, growth of *C. botulinum* may be enhanced.

In addition to MA, safety factors such as salt in combination with smoking, prevent growth of *C. botulinum* in smoked MAP fish. *C. botulinum* type E grew and produced toxin in both vacuum packed or MAP fresh and unsalted smoked slid; toxin

formation was promoted by the exclusion of O_2, but it could be prevented by MA (51.6% O_2, 47.9% CO_2, 0.5% N_2) together with a NaCl content over 3% in the aqueous phase (*5*).

Founder fillets inoculated with a mixture of spores of *C. botulinum,* packed in MA (100% CO_2 or 70% CO_2, 30% air) and held at 4.4, 10 and 26.6°C were rejected by sensory evaluation before or simultaneously with toxin detection (*6*). *C. botulinum* type E toxin was produced in vacuum packed and MAP cod and whiting fillets prior to or simultaneously with sensory rejection at 8, 12 and 26%C. However, flounder fillets were rejected prior to toxin detection at 8 and 12°C, and after toxin detection at 26°C (*7*). A narrow safety margin for *C. botulinum* growth and toxin formation in fresh salmon fillets under different MA and storage conditions was found, as toxin detection followed spoilage at 4°C, preceded spoilage at 8 and 12°C and coincided with spoilage at 30°C (*8*).

Predictive formulae to calculate the lag time prior to toxin production by *C. botulinum* type E in rockfish, salmon and sole muscle tissues, and the probability of one spore to initiate toxigenesis as a function of storage MA conditions were developed from factorial experiments. Storage temperature and spore inoculum level accounted for 74.6% and 7.4% of experimental variation, respectively, in the prediction of *C. botulinum* lag time (*9,10*).

A.hydrophila was able to grow on minced and low-salt surimi prepared from Atlantic pollock at 5 and 13°C under air or MA (51% N_2, 13% O_2, 36% CO_2), but not on salt-added surimi (*11*). Counts of *Escherichia coli* and *Staphylococcus aureus* in MAP (60% CO_2, 40% N_2) packed tuna fillets were after 5 days at 25°C approximately 10- and 100-fold lower than in fillets packed under air, but growth of *C. perfringens* and enterotoxin formulation by *E. coli, S aureus* and *C. perfringens* were not inhibited by MA(*12*).

Salmonella serotype *typhimurium* did not grow at 7°C on air packed or MA crab meat; at 11°C, MAP retarded growth. MA extended shelf-life of crab meat but did not eliminate the risk of salmonellosis under temperature abuse conditions (*13*).

Absence of *Salmonella* spp., *S. aureus* and *C. botulinum* toxin, and negligible levels of *Vibrio parahaemolyticus* were found for MAP (CO_2) gutted or filleted perch, seatrout, croaker and bluefish, which exhibited a 100-fold lower psychrotroph count than conventionally packed fish (*14*).

L. monocytogenes was isolated from channel catfish fillet strips packaged under air or 25% CO_2 atmosphere during the first two weeks of storage at 8°C, but not if a 80% CO_2 atmosphere was used or if fillet strips were held at 2°C. *Salmonella* spp. was isolated from fillet strips packaged under all atmospheres and held at 8°C, and from those packaged in air and held at 2°C.(*15*)

The National Academy of Sciences (USA) concluded that whether or not raw fish stored in modified gaseous atmospheres becomes organoleptically unacceptable before toxin can be detected depends upon a number of conditions such as fish species, film permeability, gaseous atmosphere, time-temperature profile of storage, initial number of *C. botulinum* spores, initial number of bacteria (particularly psychrotrophic spoilage bacteria), and the judgment of the evaluator (*16*).

3.2 Beef, pork, poultry and meat products

Shelf- life of minced meat was extended by MA (20-30% CO_2, 70-80% O_2), which allowed storage for 12 days at 2°C, with no growth of *Salmonella* or *S aureus* (*17*). Growth of *Salmonella, S. aureus*, enterococci and *C. botulinum* on ground beef was not enhanced by MA (*18*).

Campylobacter jejuni was able to grow on MAP beef at 37°C, but numbers naturally declined at 20°C and at 4°C at a rate which depended on the strain and on the MA, since it does not grow below 30°C (*19*). Some aerobic MA (15% CO_2, 40% O_2, 45% N_2) tested for steak storage allowed growth of *Y enterocolitica*, which was isolated after 12 days at 4°C (*20*). *L. monocytogens* and *A. hydophila* were able to grow on raw high pH beef at 10°C under a saturated CO_2 atmosphere, whereas *Y. enterocolitica* was capable of growth at 5°C *(21)*.

Numbers of *C. perfringens* and *S.typhimurium* decreased more rapidly in sliced cooked roast beef packed in MA (75% CO_2, 15% N_2, 10% O_2) stored at 4.4°C than in air, whereas numbers of *S. aureus* remained stable in MA and in air *(22)*. At storage temperatures of 12.8 and 26.7°C, all MA inhibited *S. aureus*, whereas *S. typhimurium* was relatively difficult to inhibit and increased by several log units in all MA tested;

C. perfringens was inhibited in MA with 5-10% CO_2 *(23)*.

Beef striploins steaks were inoculated with *L. monocytogenes* and vacuum packaged; counts of *L;monocytogenes* increased by 2.8 log units after 23 d at 5°C and by 3.2 log units after 11d at 10°C. Oppositely, storage of steaks under a saturated CO_2 atmosphere resulted in a reduction of *L. monocytogenes* counts at both temperatures.(*24*)

Shelf-life of sliced roast beef was extended by a saturated CO_2 CA compared to vacuum packaging from 3 to 10 weeks at 3°C, and from 8 to 16 weeks at -1.5°C. *L. monocytogenes, A. hydrophila* and *Y. enterocolitica* were able to grow on sliced roast beef at 3°C under vacuum or saturated $C0_2$ CA, whereas at -1.5°C pathogens were able to grow under vacuum but their numbers declined during incubation under CO_2 *(25)*.

C. botulinum produced toxin in inoculated MAP pork loins with initial levels of 0, 10 and 20% 0_2 at 25°C after only 2 days, but no toxin was detected in pork stored at 5°C, even after 44 days *(26)*. Toxin production by *C. botulinum* in irradiated fresh pork occurred faster in samples initially packaged with 15-30% CO_2 than with higher initial levels of CO_2 (45-75%). In most treatments, spoilage preceded toxigenesis. Inclusion of a CO_2 absorbent in the package enhanced toxin production, attributed to H_2 production by the CO_2 absorbent, which possibly resulted in a decrease in meat redox potential *(27)*. In another experiment, toxin production by *C. botulinum* at 15°C occurred faster in pork samples initially packaged with 20% CO_2 than in samples packaged with 100% N_2; all samples were spoiled before they became toxic *(28)*.

L. monocytogenes grew on pork chops packed in MA or in air more slowly than psychrotrophic bacteria, whereas *Y. entercolitica* grew more slowly in air but at the same rate in MA *(29)*.

Counts of *L. monocytogenes* Scott A in cooked tenderloin pork which was innoculated, packaged either under 100% air, 100% CO_2 or 80% CO_2 + 20% air, and stored at 4°C increased by 5log units after 18 d. Immersion of cooked pork in a solution containing 10^3 nisin IU/ml for 10 min at 20°C before innoculation with *L monocytogenes* not only prevented growth, but reduced *L. monocytogenes* counts from the beginning of the storage period by 2 log units.*(30)*

Counts of *L. monocytogenes* on MAP chicken legs treated with 10% lactic acid-sodium lactate buffer pH 3.0 remained stable for 13 days at 6°C, with an 11 days increase in shelf-life *(31)*. The proportion of *Staphylococcus* spp. and *Pseudomonas* spp. isolates decreased during storage of MAP (20-100% CO_2) ground chicken for 28 days at 2°C, with *Lactobacillus* as the predominant genus, whereas *Pseudomonas* spp. accounted for 92-98% of the isolates in air packaged chicken; an anaerobe stated to be *C. perfringens* was detected from detected from day 14 in 100% CO_2 samples and on day 28 in 20-80% CO_2 samples *(32)*. *L. monocytogenes* can increase its counts on MAP (72.5% CO_2, 22.5% N_2, 5% O_2) minced raw chicken by 6 log units after 21 days at 4°C, while this aerobic MA close to commercial practice inhibited aerobic plate counts by 4 log units *(33)*.

Growth of *L. monocytogenes* at 3, 7 and 11°C on cooked chicken loaf stored under 50% CO_2 + 10% O_2 or under 80% CO_2 was retarded by both MA in comparison to air, but these MA were not effective at inhibiting growth *(34)*. *L. monocytogenes* was capable of growth on MAP cooked chicken nuggets at 3, 7 and 11°C *(35)*. Growth of *L. monocytogenes* on MAP chicken nuggets at 3°C was stimulated by *P. fluorescens* in air and in one of the MA tested, whereas *P. fluorescens* was inhibited by *L. monocytogenes* at 11°C *(36)*. *C. jejuni* was inactivated in MAP turkey rolls by the seven MA tested, with a more pronounced effect of CO_2 on *C. jejuni* survival at 4°C (no survivors from day 18) than at 21°C *(37)*.

L. monocytogenes Scott A was able to grow on turkey roll slices packaged in air or under 30% or 50% CO_2 atmosphere (remainder N_2). Counts increased after 30 d by 1.6-2.3 log units at 4°C and by 1.3-3.8 log units at 10°C, whereas under a 70% CO_2 atmosphere (remainder N_2) *L. monocytogenes* numbers decreased by 0.6 log units at both storage temperatures.(*38*)

L. monocytogenses growth on Bruehwurst sausage (sausages boiled in broth) was inhibited by a CO_2-enriched atmosphere, but inhibition decreased with increasing temperature. At storage temperatures in the range 4-10°C, 80% CO_2 was needed to inhibit *L. monocytogenes* for 21 days, but MA caused unacceptable souring of sausages. Packaging under 50% CO_2 did not eliminate the *L. monocytogenes* hazard *(39)*. Similar results were obtained for growth of *L. monocytogenes* on MAP Frankfurter-type sausage at 4-10°C *(40)*.

3.3 Dairy products

Growth rates of *B. cereus, P. fluorescens* and a coliform in cream stored under N_2O atmosphere were reduced at 1, 4 and 7°C compared with their growth rates under air *(41)*.

Three strains of *L. monocytogenes* failed to grow at 4°C in MAP (CO_2) Cottage cheese, whereas in conventionally packed Cottage cheese their counts increased by 3 log units after 63 days. At 7°C, their counts increased by 1 log unit after 63 days in MAP Cottage cheese and by 3 log units after 14 days in conventionally packed Cottage cheese. *C. sporogenes* failed to grow in Cottage cheese.*(42) L. mnoncytogenes* Scott A was not able to grow in Cottage cheese packaged in air nor in 40% CO_2, held at 5 or 15°C.(*43*)

3.4 Vegetables and fruits

Diced raw potatoes inoculated with *C. botulinum* spores were preserved by vacuum, SO_2 (0-100%) treatment and MA (100% CO or 100% CO_2) packaging and stored for 28 days at 25°C. Neither SO_2 nor MA had sporicidal effects, and it was concluded that toxigenesis could occur without signs of spoilage *(44)*. *C. botulinum* type A inoculated (100-200 spores/g) into shredded cabbage, packaged in MA (70% CO_2, 30% N_2) and held at room temperature, was able to grow and produce toxin within 4-6 days, while the cabbage was still organoleptically acceptable; *C. botulinum* type B did not grow *(45)*.

Sliced, fresh, untreated potatoes held at 22°C were after 3d unfit for human consumption according to sensory evaluation and, if inoculated with *C. botulinum* types A or B spores, became toxic by that date. Fresh potatoes treated with $NaHSO_3$ appeared

acceptable for human consumption after 5-6d but became toxic, as $NaHSO_3$ did not inhibit outgrowth of spores and toxin production by *C. botulinum.(46)*

Fresh whole tomatoes inoculated with *C. botulinum* held at 13 and 23°C under MA (1.0-2.9% O_2) and CA (1% O_2, 20% CO_2, balance N_2) decayed and became inedible within 17-46 days depending on storage conditions, without toxin being detected. If tomatoes were held for 2-9 days after decay, toxin was detected in 4 of 5 samples *(47).*

Populations of *L. monocytogenes* increased on fresh asparagus, broccoli and cauliflower held at 4 and 15°C under air and CA. Although CA extended the length of time vegetables remained acceptable for consumption, it did not affect the growth of *L. monocytogenes.* The population of *L. monocytogenes* on asparagus stored at 4°C under CA was significantly higher after 21 days than the population on asparagus stored under air for 14 days *(48).*

Counts of *L. monocytogenes* on MAP (3% O_2, 97% N_2) shredded lettuce did not increase significantly at 5°C within 8 days, but increased from day 8 to day 15. At 10°C growth started within 3 days, and on day 10 counts reached 10^8- 10^9 cfu/g *(49). L monocytogenes* Scott A counts on shredded cabbage stored at 5°C increased by 1 log unit in air and in MA (70% CO_2, 30% N_2) withtin 13 days, whereas at 25°C counts increased by 2 log units in 2 days in air and by less than 1 log unit in MA *(50).*

Storage of fresh asparagus, broccoli and cauliflower in CA at 4 or 15°C lengthened the time vegetables were acceptable for consumption, but it did not affect the behavior of *A. hydrophila,* which survived or grew on inoculated vegetables *(51).*

E. coli O157:H7 declined on MAP (3% 02, 97% N_2) vegetables (shredded lettuce, sliced cucumber, shredded carrot) stored at 5°C, but its growth at 12 and 21°C on lettuce and cucumber for up to 14 days, without changes in visual appearance, represented a health risk (52).

Aspergillus flavus produced levels of aflatoxin over 20 ng/g in peanuts packaged in air using low, medium and high barrier films. A 65% CO_2 + 35% N_2 packaging atmosphere together with a high barrier film was effective in controlling aflatoxin production (Ellis W.O., Smith J.P., Simpson B.K., Ramaswamy H., Doyon G., 1994a; Food Res. Int. 27, 505). A 5-15% O_2 headspace concentration in MAP peanuts allowed in most cases extensive growth of *A. flavus* and production of over 20ng/g aflatoxin after 1 week at 20-30°C and a_W of 0.91-0.97.*(53)*

3.5 Miscellaneous

Food-borne pathogens were isolated from 10 out of 58 lots of refrigerated low-acid MAP foods, mainly sandwich-type products. *L. monocytogenes* was present in 5 lots, other *Listeria* spp. in 3 lots, *A. Hydrophila* in 1 lot and *S. aureus* in 1 lot; *Salmonella* and *C. botulinum* were not detected *(54)*.

S. aureus was detected in 17.5% of plain and in 33.7% of filled fresh and frozen MAP pasta products, and *E. coli* in 4.3% and 24.2%, respectively *(55)*.

4. Conclusions

The microbiological safety of MAP and CAP foods depends on factors such as microbiological quality of the initial product, hygiene of manufacturing practices, inherent or added preservation parameters, appropriateness of packaging material and equipment, adequacy of gaseous atmosphere, maintenance of refrigeration temperatures and correct handling of the finished product until expiration date.

Most pathogens do not grow or survive better in MA or CA than in air, but some strains of *Clostridium* may do so at refrigeration temperatures and also certain strains of *Campylobacter* at temperatures exceeding 30°C. However, as MA and CA delay the rate of spoilage, pathogens present at the same level in the initial product may reach in MAP and CAP foodstuffs higher populations than in conventionally packaged products before the respective expiration dates.

In the particular case of fish, the final statement of the National Academy of Sciences must be recalled. " Thorough studies are needed to evaluate the potential hazard of refrigerated storage of raw fish in vacuum packages and in modified gaseous atmospheres. Until such time that the safety of this storage method for raw fish is validated, this practise is not recommended by this subcommittee because of its potential health risks " *(16)*

Modified atmospheres have been proven to enhance product quality by inhibiting spoilage bacteria, and may also constitute a hurdle to the growth of some pathogens. In fact, MAP and CAP foods show a goos safety record during the last decade. However, temperature abuse can occur at any point during the storage, distribution, display or consumer handling of MAP or non-MAP refrigerated foods. The longest the shelf-life of foods, the highest the probability that temperature abuse may happen and that pathogens may grow. Realistic decisions on the expiration date of MAP foods, taking into consideration mainly food safety aspects and not only food organoleptic quality aspects and being coherent with EU microbiological standards, are needed in order to protect the health of consumers.

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ANNEX

Some Practical Recommendations

For the food industry

1. Make sure that products likely to be stored under conditions supporting the growth of pathogens are designed so that these organisms are either inhibited or killed.
2. Make sure that product shelf-life is based on a realistic estimate of temperatures that the product is likely to be stored at during distribution and in the home.
3. Make sure that the " use by " date is clearly indicated on the food package.
4. Make sure that the correct storage temperature is clearly indicated on the food package
5. Make sure that there is a clear warning against temperature abuse on the food package.

For the consumer

1. Make sure to comply with storage conditions indicated on the package.
2. Do not consume MAP and CAP foods after the " use by " date.
3. Be aware that the " use by " date indicated on the package is ONLY applicable to foodstuffs in the UNOPENED INTACT package, stored at the INDICATED TEMPERATURE.
4. Be aware that the absence of microbioligocal spoilage and organoleptic changes is not a reliable indicator for the safety of MAP and CAP foods.

OPINION ON PROPANE-1,2-DIOL

(Expressed on 20 September 1996)

Terms of reference

To re-evaluate the safety-in-use of propane-1,2-diol (propylene glycol) in the light of additional mutagenicity studies.

Background

The Scientific Committee for Food (SCF) reviewed the safety-in-use of propane-1,2-diol (propylene glycol) at its plenary meeting of December 1993. The uncertainty with regard to potential clastogenic effects at germ cell level, as well as the absence of a carcinogenicity study in a second species, led the SCF to change the full ADI into a temporary ADI of 25 mg/kg b.w. To clarify the existing doubts, the Committee recommended an in vitro mouse lymphoma cell assay or two in vitro assays at gene and chromosome level in mammalian cells (1).

Evaluation of additional mutagenicity studies

The following additional studies were made available by industry.

Propane-1,2-diol has been tested for its ability to induce chromosome aberration in human lymphocytes cultured in vitro, with and without exogenous metabolic activation (S9 mix), at concentrations of 476, 1910 and 3910 μg/ml. Propane-1,2-diol was found to be devoid of clastogenic activity (2).

Propane-1,2-diol was tested for various genetic endpoints in several test systems both in vitro and in vivo. These were: gene mutation in strains G-46 and TA1530 of S. typhimurium, mitotic recombination in strain D3 of S. cerevisiae by "Host Mediated Assay" in mice orally treated at dosages of 30, 2,500 and 5,000 mg/kg b.w., chromosome aberration in human embryonic lung cells (Wi-38) cultured in vitro, chromosome aberration in bone marrow cells of rats treated orally with doses of 30, 2500 and 5000 mg/kg b.w. and, dominant lethal mutation in rats treated orally with at doses of 30, 2500 and 5000 mg/kg b.w..

Under the experimental conditions used propane-1,2-diol was negative, with the exception of some recombinogenic activity shown in S. cerevisiae. (3).

Conclusion

The additional information provided does not correspond entirely to the SCF's request (an in vitro mammalian gene mutation assay is still lacking). However, taking account of the results obtained in the above mentioned assays, as well as the results of several in vitro and in vivo genotoxicity studies reviewed in the previous report (1), it can be concluded as an overall evaluation that propane-1,2-diol does not pose a significant concern for genotoxic potential.
The Committee concludes that a full ADI of 0 - 25 mg/kg b.w. can be reassigned to propane-1,2-diol.

References

1. Report of the Scientific Committee for Food on Propylene glycol (35th series); Commission of the European Communities (1996). [Opinion expressed on the 9 Dec 1993]

2. Metaphase chromosome analysis of human lymphocytes cultured in vitro; Huntingdon Research Centre Ltd, Report N° CLD 49/90349, June 1990.

3. Mutagenic evaluation of compound FDA 71-56-Propylene Glycol; Litton Bionetics, prepared for the US-FDA, Report PB-245-450, 5 March, 1974.

SCF OPINIONS ON THE ASSESSMENT OF NOVEL FOODS
II
Recommendations concerning the scientific aspects of the presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients
(expressed on 13 December 1996)

Introduction

In part I of the *SCF Opinions on the Assessment of Novel Foods* recommendations concerning the scientific aspects of information necessary to support applications for placing on the market of novel foods and novel food ingredients (NF) have been presented. In this part recommendations concerning the scientific aspects of the presentation of such information are summarized. Such a uniform structure of applications will facilitate their scientific evaluation.

General scheme

It has been emphasised in the first part of the recommendations that no formalistic approach can adequately cover all NF. Thus, the schemes developed are not to be considered as rigid checklist but are provided for guidance only. Nevertheless, the underlying philosophy and the major principles of the recommendations should be reflected in an application for placing on the market of NF. The following box illustrates the logic flow.

General description of the NF including technical data and catergorization according to the EU regulation

⇓

Allocation of the NF to one of the SCF classes/subclasses

⇓

Identification of essential information requirements

⇓

Consultation of structured schemes (decision trees) and provision of data required

⇓

Evaluation and conclusion by the applicant

The information package submitted by the applicant should be presented in the order and under the headings described below:

1. Administrative data

This section should include information on name and address of the applicant, of the manufacturer of the NF and of the person responsible for the dossier.

2. General description

In order to ensure that the food or food ingredient intended to be placed on the market falls within the scope of the EU Regulation on Novel Foods and Novel Food Ingredients, data should be provided to enable a catergorization according to Art. 1 (2) of the EU regulation.
To facilitate the assessment procedure the SCF has reclassified the diverse categories defined by the legislation according to their similarities in terms of safety considerations. Six major classes and corresponding subclasses are defined in chapter 4 of the *SCF Opinion on the Assessment of Novel Food, Part I* (later referred to as *Part I*). The NF should be allocated to one of these classes/subclasses (see also Table I, *Part I*); the scientific justification for this allocation should be given.

3. Identification of essential information requirements

Table II, *Part I* should be used to determine which of the schemes I-XIII are essential to provide data permitting a safety and nutritional evaluation of the NF.

4. Consultation of structured schemes (decision trees)

The structured schemes I-XIII elaborated in *Part I* should be consulted regarding the data to be assembled. The schemes lead through a decision tree-like set of questions and will assist in the decision whether the data available to the applicant are sufficient or if further information has to be sought and reappraised.

The logic of the schemes should be followed in the dossier. For each box the information leading to either "yes" or "no" should be provided in detail. If it is proposed to omit certain information requested in any of the schemes, the scientific justification should be given. If other information is available or considered to be relevant for the assessment, it should be submitted.

5. Evaluation and conclusion by the applicant

Conclusions drawn by the applicant after having evaluated the total information assembled should be presented covering the key issues relevant to the NF (see chapter 3 of *Part I*).

6. Summary by the applicant

A summary has to be provided that is suitable for further circulation to the Member States as foreseen in Art. 6 (2) of the EU regulation.

SCF OPINIONS ON THE ASSESSMENT OF NOVEL FOODS
III
Recommendations concerning the scientific aspects of the preparation of the initial assessment reports on applications for placing on the market of novel foods and novel food ingredients
(expressed on 13 December 1996)

Introduction

The EU Regulation on Novel Foods and Novel Food Ingredients stipulates in Article 4 that a person responsible for placing on the Community market such a product submits a request for this action to the Member State in which the product is to be marketed for the first time. According to the provisions of Article 6 the Member State must then prepare an initial assessment report.

Part I of the SCF Opinions on the Assessment of Novel Foods presents recommendations concerning the scientific aspects of information necessary to support applications for placing on the market of novel foods and novel food ingredients (NF). Part II summarises recommendations concerning the scientific aspects of the presentation of such information.

Some experience in assessing the safety of novel foods has been gained by applying procedures of various national and international bodies and authorities. For practical purposes it is necessary to achieve comparability between assessments by different national authorities and also uniformity in the reports of their scientific appraisals. Details of the requirements for particular types of NF are provided in Part I and elsewhere, e.g.: with regard to products produced by genetic modifications (1); or other novel sources of protein (2). Specific recommendations for safety testing have not been made for each class of NF and it is not possible to do so in the current state of knowledge. The use of a case-by-case approach ensures that novel risks are adequately addressed. Part III is intended to provide guidance for this task and therefore contains recommendations concerning the scientific aspects of the preparation of the initial assessment reports by the competent authorities of the Member States.

Structure of the initial assessment report

The general considerations underlying the assessment of NF have been set out in Part I, e.g. Section 3.1. Initial assessment reports are confined to the human food safety of NF, their preparation should proceed in the following three phases:

1. Check of the completeness of the application and its presentation in accordance with Part II.
2. Appraisal of appropriateness of interpretations and evaluations by the applicant of the data

submitted.
3. Assessment of the data submitted, executive summary, conclusions and recommendations.

1. Check of the completeness of the application and its presentation in accordance with Part II

The initial assessment report must provide a statement that the submission contains the appropriate administrative and technical details presented in the order laid down in Part II, Section 1 and 2, as well as the information set out in Part I, Section 5 and 5.1. If the data submitted differ from those requested in Part II or are not presented in the order required, the applicant's explanation should be reviewed.

2. Appraisal of appropriateness of interpretations and evaluations by the applicant on the data submitted

The adequacy of the data and of the arguments relating to their interpretation and evaluation by the applicant should be assessed and an opinion provided. In the event of disagreements in the interpretations and evaluations between the national assessing authorities and the applicants the pertinent reasons should be fully described in the assessment report.

2.1 Substantial equivalence

For assessment purposes the comparison of the final product with one having an acceptable standard of safety furnishes an important element. Therefore, the initial assessment report should include the competent authority's opinion regarding the applicant's claims concerning substantial equivalence.

2.1.1 Substantial equivalence to a traditional counterpart is claimed

For guidance the relevant discussion in Part I, Section 3.3 should be consulted. If substantial equivalence to a traditional counterpart has been established, the NF can be regarded as wholesome and as toxicologically and nutritionally acceptable for use in the overall diet in a manner comparable to its counterpart or as replacement of its counterpart. When judging the comparability of the NF to its counter part, the limits of known and measurable natural diversity of any conventional counterpart should be taken into account.

2.1.2 Substantial equivalence except for one or more defined traits is claimed

If substantial equivalence except for one or more defined traits has been established, the assessment should focus on these traits. These should be evaluated on a case-by-case basis and may in certain cases require data, matching those needed for the safety evaluation of food additives.

2.1.3 Substantial equivalence is not claimed

If substantial equivalence to a traditional food or food ingredient is not claimed, the NF will require extensive testing details of which are outlined in Part I.

2.2 Special considerations

For foods that are substantially equivalent to existing foods no further data need to be evaluated. Other NF require further consideration. This may be targeted at specific defined traits or at the whole NF. The information provided in the application will need to be assessed in the light of the origin, method of production and complexity of the NF, and its role in the diet of the population at large and particular sub-groups.

2.2.1 Nutritional assessment

Special attention should be paid to the expected consumption level of the NF and its potential nutritional impact (see Part I, e.g. Section 3.8 and Section 5.XI). It should be checked, for example, that the effects of the consumption of the NF on the total dietary intakes of nutrients, for which PRI's (population reference intakes) or an "acceptable range of intakes" have been established, have been assessed within specific population groups.

The competent authority should evaluate the documentation on animal models and human metabolic studies, including clinical observations. Long term as well as short term effects of the NF on human nutrition have to be considered. Attention should be paid to the occurrence of unexpected adverse interferences with other dietary constituents and to changes in relevant biomarkers.

2.2.2 Assessment of novel microorganisms for food use

For NF which are or which contain live microorganisms, scrutiny by the authority should confirm, that the application contains adequate data on their safety in use. Even with microorganisms the data submitted should allow them to be categorised according to the principle of substantial equivalence (see also Part I).

2.2.3 Assessment of toxicity and allergenicity

The evaluation will need to address - as appropriate - data on toxicity and allergenicity regarding defined traits of the NF or the entire NF. The information necessary to assess the wholesomeness of NF has been discussed in Part I, e.g. Sections 3.7, 3.10 and 5.XIII. The application should be scrutinized for the adequacy of the data presented and an opinion on the data should be formulated.

2.2.4 Novel Processes

Products of novel processes should be evaluated on the basis of the concept of substantial equivalence (see also Part I and II).

3. Assessment of the data submitted, executive summary, conclusions and recommendations

The assessment report should included an opinion on the adequacy and completeness of the data provided. The competent authority should prepare an executive summary. The assessment report should be accompanied by a statement on its conclusions and recommendations including any conditions for marketing. In addition, benefits claimed by the applicant as well as pitfalls should be described and discussed briefly.

4. References

1. Biotechnology and Food Safety. The Report of a joint FAO/WHO Consultation, 1996

2. PAG/UNU Guidelines

European Commission

Reports of the Scientific Committee for Food
(fortieth series)

Luxembourg : Office for Official Publications of the European Communities

1997 : v, 70 pp. - 16,2 x 22,9 cm

food — science and techniques series

ISBN

Price (excluding VAT) in Luxembourg : ECU

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), replaced by Commission Decision 95/273/EC of 6 July 1995 (OJ, L 167, 18.7.1995, page 22), to advise the Commission on any problem relating to the protection of the health and safety of persons arising or likely to arise from the consumption of food, in particular on nutritional, hygienic and toxicological issues.

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

Responsibility for the Secretariat of the Scientific Committee for Food was transferred from Directorate General III "Industry" to Directorate General XXIV "Consumer Policy and Consumer Health Protection" with effect from 1st April 1997.

The present report deals with:

* Endocrine disruptors and food
* Additives in nutrient preparations for use in infant formulae, follow-on formulae and weaning foods
* Opinion on Bisphenol A Diglycidyl Ether
* The potential risk to human health arising from the transport in ships' tanks of oils and fats from substances proposed as acceptable previous cargoes
* The microbiological safety of modified-atmosphere packaged (MAP) and controlled-atmosphere packaged (CAP) foods
* Propane-1,2-diol
* The assessment of novel foods
  - part ii: recommendations concerning the scientific aspects of the presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients
  - part iii: recommendations concerning the scientific aspects of the preparation of the initial assessment reports on applications for placing on the market of novel foods and novel food ingredients