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Opinion of the Scientific Committee on Food on

Impurities of 1,4-dioxane, 2-chloroethanol and mono- and diethylene glycol in currently permitted food additives and in proposed use of ethyl hydroxyethyl cellulose in gluten-free bread

(expressed on 4 December 2002)

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Terms of reference

The Committee is asked to re-evaluate the safety in use of the selection of food additives as listed below in view of the potential presence of ethylene oxide, 1,4-dioxane and mono- and diethylene glycol as impurities.

In the light of the Committee's evaluation, the Commission will consider taking any necessary legal steps for the amendment of the Community legislation on food additives.

The Committee is also asked to reconsider the safety in use of ethyl hydroxyethyl cellulose as a food additive previously evaluated by the Committee on 24 March 1999 (SCF, 1999), in the light of additional information, in particular regarding the potential presence of impurities such as ethylene oxide, 1,4-dioxane, ethylene chlorohydrin and mono- and diethylene glycol.

Table 1: Purity criteria for polysorbates and EHEC

E No	Name	Purity criteria			
		Ethylene oxide	1,4-dioxane	2-chloro-ethanol	Ethylene glycols (mono- and di-)
E 431	Polyoxyethylene (40) stearate[1]	≤ 1 mg/kg	≤ 5 mg/kg	ns[3]	≤ 0.25%
E 432-436	Polyoxyethylene sorbitan esters (polysorbates)[1]	≤ 1 mg/kg	≤ 5 mg/kg	ns[3]	≤ 0.25%
E - INS 1521	Polyethylene glycol 6000[1]	≤ 1 mg/kg	ns[3]	ns[3]	ns[3]
INS 467 (not in EU)	Ethyl hydroxyethyl cellulose[2] (EHEC)	≤ 0.5 mg/kg	≤ 0.5 mg/kg	≤ 0.5 mg/kg	≤ 1%

1) Commission Directive 98/86/EC of 11 November 1998, OJ L 334, 9.12.1998, p. 1 (http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav14_en.pdf)
2) JECFA specification prepared at the 49th JECFA (1997), published in FNP 52 Add 5 (1997) (http://apps3.fao.org/jecfa/additive_specs/docs/5/additive-0659.htm)
3) ns = not specified

Background

The modified cellulose, ethyl hydroxyethyl cellulose (EHEC), when previously evaluated by the Scientific Committee on Food (SCF) was included in the Acceptable Daily Intake (ADI) "not specified" already allocated for five other modified celluloses (SCF, 1999). Its proposed authorisation was subsequently questioned by the European Parliament (2000) because of the possible presence of impurities such as ethylene oxide and 1,4-dioxane, which have been classified as 'carcinogenic to humans (Category 1)' and 'possibly carcinogenic to humans (Category 2B)', respectively, by the International Agency for Research on Cancer (IARC, 1994, 1999). Accordingly, it is not yet authorised for use in the EU pending re-evaluation by the SCF. The five other modified celluloses already approved by the SCF and authorised for use in the EU are made from different starting materials and do not contain these impurities. It was realised that some other, already permitted additives also could contain these impurities and they were therefore also included in this survey.

An opinion on ethylene oxide was given by the Committee on 17 April 2002 (SCF 2002) and the present paper will therefore address only the question on the other impurities.

Exposure estimates

From use of ethyl hydroxyethyl cellulose (EHEC)

Originally EHEC was accepted by the SCF for general use in line with the other permitted cellulose derivatives, i.e. *quantum satis* (SCF, 1999). Following the questions from the European Parliament the request by the petitioner was reduced to use only in gluten-free bread with a maximum use level of 0.5% (5g/kg) in dry bread mixture, equivalent to about 3g EHEC/kg bread (OFCA 2000)

In a survey carried out in the Scientific Cooperation (SCOOP, 1996) it was concluded that the mean consumption of bread and ordinary bakery ware in various EU Member States was between 99 and 254 grams per day (133g in Belgium, 144 g in France, 228 g in Greece, 133 g in Ireland, 158 g in Italy 127 g in Netherlands, 254 g in Portugal, 141 g in Spain, 99 g in Sweden and 107 g in UK. In Norway it is 197g per day). As these figures are mean values the Committee chose a figure of 300 g/day as a reasonable estimate to cover high consumers. A daily intake of 300 g of bread containing the maximum requested level of 3g/kg would result in an expected maximum intake of about 1g EHEC/person/day. This would mean that the maximum intake of the substances in question would be 0.5 μg each of 1,4-dioxane and 2-chloroethanol and 10 mg of the glycols, per person per day, if these substances were present up to the maximum limit. These intakes are equivalent to 0.008 μg/kg bw/day for 1,4-dioxane, 0.008 μg/kg bw/day for 2-chloroethanol, and 0.17 mg/kg bw/day for the glycols, for a 60 kg person.

From use of polyoxyethylene sorbitan esters (polysorbates) (E 432-6)

The polysorbates are permitted in various foods according to the European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners (European Commission, 1995) as shown in Table 2.

In the EU food additive monitoring system it was estimated that with the presently permitted use levels and based on food consumption patterns in various Member States the intake of the polysorbates could be up to the ADI, i.e. 10 mg/kg bw/day (European Commission 2001). This means that if 1,4-dioxane were present up to the permitted maximum level, the exposure could be up to 0.05 μg/kg bw/day. For the ethylene glycols the comparable figure would be 25 μg/kg bw/day.

Table 2: Permitted uses of polysorbates in foods

Food	amount in g/kg Individually or in combination
Fine bakery wares	3
Fat emulsions for baking purposes	10
Milk and cream analogues	5
Edible ices	1
Desserts	3
Sugar confectionery	1
Emulsified sauces	5
Soups	1
Chewing gum	5
Dietary food supplements	*quantum satis*
Dietetic foods intended for special medical purposes – Dietetic formulae for weight control intended to replace total daily food intake or an individual meal	1

From use of polyoxyethylene(40)stearate (E431)
This additive is only permitted in some imported wines in levels not exceeding 18 mg/L (FDA) and the exposure of the impurities from this source is therefore considered insignificant compared to the total exposure from other sources.

Review of the substances

1,4 dioxane

When the SCF evaluated 1,4-dioxane as a component of food contact materials, this substance was listed in List 6A (substances suspected of having carcinogenic properties and should not be detectable in foods or in food simulants) (SCF 1986). The Committee also found the substance not acceptable as an extraction solvent (SCF 1992), mainly because of lack of sufficient data together with suspicion of toxic effects.

IARC has classified dioxane in group 2B - possibly carcinogenic to humans (inadequate evidence for carcinogenicity in humans and sufficient evidence in animals) (IARC 1999). IARC states that most of the broad range of tests for genotoxic activity have produced negative results, but positive results were obtained in a cell transformation assay and conflicting results were obtained in mouse bone marrow cell tests for micronucleus induction.

A Risk Assessment Report has been prepared in the context of Council Regulation 793/93 on the evaluation and control of existing substances. The version dated 5 November 1999 was reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) at its 19th meeting on 9 November 2000 (CSTEE, 2000). The Committee had several comments but agreed on the final conclusion that 1,4-dioxane is a carcinogen in experimental animals, but it is not genotoxic and therefore a threshold approach is appropriate. At low doses the substance is rapidly metabolised to β-hydroxyethoxy acetic acid (HEAA) and 1,4-dioxane-2-one. At higher doses (10-100 mg/kg bw/d) this metabolism is saturated, resulting in decreased urinary excretion of metabolites and increased 1,4-dioxane in expired air. Also a shift in the ratio of oxidation products HEAA and 1,4-dioxane-2-

one to the possible reactive intermediate products 1,4-dioxane-2-ol and β-hydroxyethoxy acetaldehyde is proposed.
The Risk Assessment Report (European Commission, 2002) concluded from the mutagenicity data that "*in vitro*, clastogenic and mutagenic effects were not reported. *In vivo*, a dominant lethal test was negative and in a test for sex linked recessive lethal mutations in *Drosophila melanogaster* positive results were obtained. From 6 performed micronucleus tests one oral test with C57BL6 mice showed a positive result. Three other oral tests using C57BL6 mice, BALB/c, and CBA mice and two intraperitoneal tests with B6C3F1 and CD-1 mice showed negative results. In 4 of these negative tests the target organ was reached. *In vitro* as well *in vivo* alkaline elution tests pointed to DNA strand breaks at high dose levels. 1,4-Dioxane can also induce sister chromatid exchanges in CHO cells and cell transformation in Balb/3T3 cells. Although there are some indications that 1,4-dioxane may be weakly genotoxic, 1,4-dioxane is considered a non-genotoxic compound based on the total weight of evidence. This is further supported by the absence of DNA-adducts at hepatotoxic doses."

The Risk Assessment Report (European Commission, 2002) summarised the carcinogenicity data as follows. "From chronic drinking water experiments with rats and mice it can be concluded that 1,4-dioxane causes liver and kidney damage and liver adenomas and carcinomas. Furthermore, in rats nasal adenomas and carcinomas were also seen, accompanied by non-neoplastic lesions in the nasal cavity. These lesions were also observed in mice, but in mice 1,4-dioxane did not induce an increased incidence of nasal tumours.

The liver, kidney and nasal damage were seen at concentrations of 0.02%, 0.1% and 0.1% respectively, in drinking water, while at 0.01% (equivalent to 10 mg/kg bw/day) no effects were seen. The liver tumours were seen at 1,4-dioxane drinking water concentrations of ≥0.05% for mice and ≥0.1% for rats. The nasal tumours in rats were observed at 1,4-dioxane drinking water concentrations of ≥0.5%. Some indication for liver tumours were also obtained in guinea.pigs, but no information on non-neoplastic lesions was provided. Based on these results, 1,4-dioxane can be considered as a carcinogen for test animals. Since 1,4-dioxane is considered a non-genotoxic compound a threshold approach seems justified. The liver tumours are considered to be associated with cytotoxicity and organ damage, which seem to occur in particular at dose levels at which 1,4-dioxane metabolism becomes saturated. The nasal tumours cannot be explained from a drinking water study, however, it seems that nasal toxicity plays a role in the nasal carcinogenicity. The overall NOAEL, based on liver damage, can be considered to be 0.01% (equivalent to 10 mg/kg bw/day)." (European Commission 2002).

2-chloroethanol (ethylene chlorohydrin)

According to Patty (1994), 2-chloroethanol is a reaction product of ethylene oxide with chloride. It can be absorbed by the oral, dermal, or inhalation routes of exposure, but quantitative data are limited. It has a moderate to high order of acute toxicity (figures from 71 to 110 mg/kg bw have been quoted). Repeated oral exposure resulted in histopathological effects in the liver and lung in rats receiving doses of 67.5 mg/kg by gavage up to 90 days, and mortality was increased. Rats receiving 30 or 45 mg/ kg showed no treatment related effects (Oser et al., 1975). Doses of more than 20 mg/kg bw/day in the diet to dogs was followed by severe emesis while 15 mg/kg was without effect. Monkeys receiving up to 62.5 mg/kg bw showed no noteworthy differences from the controls. Gross and histopathological examinations disclosed no consistent dose-related abnormalities in any of the species (Oser et al., 1975).

2-Chloroethanol was not carcinogenic when given in the drinking water to rats up to 16 mg/kg bw for up to 2 years (Roxon et al., 1967). In a study from National Toxicology Programme (NTP), rats

and mice received dermal doses of 50 or 100 mg/kg bw for 2 years without evidence of carcinogenicity. Foetotoxicity and maternal toxicity in mice have been observed from 2-chloroethanol exposure by gavage, 150 mg/kg bw being maternally lethal and a lower dose of 50 mg/kg had no consistent effect (quoted from Patty, 1994). Teratogenicity was observed only in mice given 2-chloroethanol intravenously at maternally toxic doses of 120 mg/kg bw while no effects were seen at 60 mg/kg bw. No effects were seen in rabbits receiving up to 36 mg/kg bw which was the maximum tolerated dose (Laborde et al., 1982)

The mutagenicity data show that 2-chloroethanol has been found to be active (generally weakly so) in several *in vitro* tests. These include tests for gene mutation in *Salmonella typhimurium* reversion strains detecting base pair substitution, with and without S9 (Malaveille et al., 1975; Rosenkranz et al., 1974; Bartsch et al., 1975; Bignami et al., 1980; McCann et al., 1975; Tennant et al., 1987), tests for DNA damage in *Escherichia coli*, without S9 (Rosenkranz et al., 1974), tests for gene mutation, recombination and aneuploidy in *Aspergillus nidulans*, without S9 (Bignami et al., 1980; Crebelli et al., 1984), tests for gene mutation in mammalian cells (Chinese hamster ovary cells and mouse lymphoma assay), with and without S9 (Tennant et al., 1987; Flowers et al., 1988; McGregor et al., 1988), and tests for chromosomal aberrations and sister chromatid exchanges, with and without S9 (Tennant et al., 1987; Ivett et al., 1989). *In vivo*, 2-cholorethanol has been found to be negative in several genotoxicity assays in rodents. These include rat oral gavage tests for micronucleus formation in bone marrow and hepatocytes and for unscheduled DNA synthesis in liver (Allavena et al., 1992), and intraperitoneal mouse bone marrow micronucleus and chromosomal aberration tests (NTP studies cited in Shelby et al., 1993; 1995). It was also negative in rat and mouse chronic toxicity/carcinogenicity studies by skin painting (NTP Report 275 cited in Shelby et al., 1995). Thus the available data suggest that 2-chloroethanol is a weak, genotoxic agent *in vitro*, devoid of detectable effects *in vivo*.

Mono- and diethylene glycol

These substances have been evaluated by the SCF as components in food packaging materials. A group TDI of 0-0.5 mg/kg bw was allocated (SCF, 1986). An up-to-date search in Medline/Toxline revealed no data which would suggest any change was necessary in this group TDI. Mono- and diethylene glycol are found in foods as migrants from the use of regenerated cellulose film (RCF). A 1988 survey of the main foods wrapped in RCF (chocolates, boiled sweets, toffees, cakes and meat pies) showed migration values to be between 10 and 50 mg/kg of food. The use of RCF has declined since that time. (Castle et al., 1988).

Conclusions

1,4-Dioxane: Although feeding studies in animals indicate that 1,4-dioxane is a carcinogen in laboratory animals it is concluded that it is acting by a non-genotoxic mechanism based on the essentially negative results of several *in vitro* and *in vivo* genotoxicity assays, the lack of significant DNA-binding *in vivo* in mice treated with ^{14}C-labelled 1,4-dioxane and the fact that the tumours are associated with chronic toxicity in the target organs. Thus a threshold approach can be applied. The estimated potential maximum exposure of 1,4-dioxane from the proposed use of EHEC in bread and from the permitted use of the polysorbates is 0.008 and 0.05 microgram/kg bw/day, i.e. about 170,000 times lower than the NOAEL of 10 mg/kg bw and is therefore of no toxicological concern.

2-Chloroethanol: 2-Chloroethanol is not carcinogenic to laboratory animals and is not genotoxic *in vivo*. Thus a threshold approach can be applied. Doses found to have other toxicological effects are in the mg/kg range while the estimated potential maximum exposure to 2-chloroethanol from the

proposed use of EHEC in bread is 0.008 microgram/kg bw/day and is therefore of no toxicological concern.

Mono- and diethylene glycol: The estimated potential maximum exposure of mono- and diethylene glycol from the proposed use of EHEC in bread and from the permitted use of the polysorbates is less than 0.2 mg/kg bw/day, which is well within the existing TDI of 0-0.5 mg/kg bw. Given the other sources of mono- and diethylene glycol in food are from very limited use of regenerated cellulose film as wrapping material, the TDI is unlikely to be exceeded.

Thus the present purity criteria for the currently permitted food additives E432-436 (**polysorbates**) are appropriate for the protection of consumer health.

Ethyl hydroxyethyl cellulose (EHEC) has been requested for use in gluten-free bread in an amount of up to 5 g EHEC/kg in dry bread mixture, resulting in about 3 g EHEC/kg final bread. The data available on the toxicity and worst case estimates of exposure to the residues in EHEC of 1,4-dioxane, 2-chloroethanol (ethylene chlorohydrin) and mono- and diethylene glycol show that the proposed maximum levels of 0.5 mg/kg, 0.5 mg/kg and 1% respectively are of no toxicological concern.

The Committee concluded that EHEC is acceptable for use in gluten-free bread, with the residue limits proposed for the substances evaluated in this report, and provided that residues of ethylene oxide are below the current limit of detection, as recommended in the opinion expressed by the Committee on this impurity (SCF 2002).

This opinion should be read in conjunction with the Committee's previous opinion on EHEC (SCF 1999) but it should be noted that the ADI "not specified" allocated in 1999 has been replaced by the above restrictions.

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