Compendium of food additive specifications (Annex 1, references *96*, *103*, *109*, *118*, *124*, *133* and *139*) are designated as "tentative", indicating that some information or data were missing or incomplete at the time the specifications were prepared. Some of these specifications have been designated as "tentative" for more than 30 years, and often no reason is given for this designation. Newer specifications include the reasons.

The Committee prepared two lists of the existing tentative specifications for food additives, excluding flavouring agents. The first list comprises specifications that do not include the reasons for the "tentative" designation, while the second contains the remaining tentative specifications, with the reasons for the designation.

The lists will be included with the call for data for the fifty-fifth meeting of the Committee, to be held in 2000. Technical data and information on the present uses of the additives in foods will be requested. If no data are received or if the substance is no longer used in foods, the tentative specifications will be withdrawn. Technical data and information on the reasons for all tentative designations will also be requested.

2.6.5 *Tentative specifications for flavouring agents*

At its forty-sixth, forty-ninth and fifty-first meetings (Annex 1, references *122*, *131* and *137*), the Committee developed specifications for the purity of over 400 flavouring agents, of which about one-quarter were designated as "tentative" because certain necessary information was lacking. In making these designations, the Committee relied on its judgement rather than on a carefully defined system. At its present meeting, the Committee agreed that it was important to be consistent in applying tentative designations and agreed that specifications submitted for consideration should be designated as "tentative" if information had not been provided on:

- chemical formula and relative molecular mass, identity test, and the minimum amount that can be determined (minimum assay value);
- the additional criteria related to purity, including boiling-point (for liquids), melting-point (for solids), refractive index (for liquids) and specific gravity (for liquids).

The Committee will, however, consider attributing full specifications when the absence of one or more of the additional criteria related to purity can be justified.

In order to ensure consistency, the Committee agreed that the specifications for the flavouring agents evaluated at its forty-sixth, forty-ninth and fifty-first meetings should be re-examined by the same approach. As a result, the tentative designation for the specifications for one of the flavouring agents (no. 8, allyl sorbate) was removed, and the specifications for over 50 other flavouring agents were given "tentative" designations. Although some of these flavouring agents, such as acetaldehyde and acetic acid, are well characterized, they were given tentative designations because not all of the information required to satisfy the criteria set out above regarding their use as flavouring agents was included in the material submitted. Overall, about one-third of the specifications for flavouring agents developed at the previous three meetings were designated as "tentative". The Committee agreed that flavouring agents submitted for evaluation at future meetings would not be considered for specifications unless the minimum information set out above was provided.

The Committee concluded that its first priority was to seek further information on the tentative specifications; however, it will also re-examine specifications that are not designated as "tentative" but for which the minimum assay values are less than 95%, and these will be included in future calls for data. The Committee further agreed that the relevant data should be sought in time for review at its fifty-fifth meeting to be held in 2000, and the flavouring agents on which data are sought will be included in the call for data for that meeting. If these data are not supplied, the specifications will be withdrawn.

2.7 Evaluation of substances as food additives that are also food ingredients or natural constituents of food

The Committee noted that some substances can be used both as ingredients of food and as food additives (e.g. polyols and turmeric), and that some substances used as food additives occur naturally in foods (e.g. carotenes and some flavouring agents). The Committee reaffirmed that its risk assessments clearly identify whether a substance is being evaluated only as a food additive or for additional uses, such as a food ingredient, and that the relative contribution of use as a food additive to total intake is identified when possible. When other food uses of the substance are known the assessment will clearly state whether all routes of intake have been evaluated. The Committee noted that numerical ADIs refer to exposure from all sources.

3. Specific food additives and substances used in food fortification

The Committee evaluated three food additives for the first time and re-evaluated two food additives and one substance used in food fortification programmes considered at previous meetings. Information on the evaluations and on specifications is summarized in Annex 2. Details of further information required for certain substances are given in Annex 3.

3.1 Glazing agent: hydrogenated poly-1-decene

Hydrogenated poly-1-decene is a mixture of synthetic branched-chain hydrocarbons (isoparaffins) which are produced by oligomerization of 1-decene to the tri-, tetra- and penta-decene molecules, followed by hydrogenation to full saturation of the oligomer. Hydrogenated poly-1-decene has been proposed for use in foods as a substitute for white mineral oil when it is used as a glazing or polishing agent for dried fruits and certain sugar confectionery, such as fruit gums and jellies. Hydrogenated poly-1-decene is also used as a release ("non-stick") coating in bread tins, as a lubricant in dough-dividing machines, as an anti-dusting and anti-foaming agent and as a plasticizer in films that come into contact with food.

Since hydrogenated poly-1-decene is a synthetic product, its composition is well defined. The oligomer distribution of the product is 16–35% trimers, 42–61% tetramers, 12–23% pentamers and 1–9% hexamers; the dimer concentration is less than 1%.

Hydrogenated poly-1-decene was previously evaluated by the Committee at its forty-ninth meeting (Annex 1, reference *131*), when the data available from two studies of 28 and 90 days' duration in rats given repeated doses were reviewed and considered to be inadequate to support the use of this product as a food additive. In view of the potentially high intake of this compound, the Committee concluded that adequate data were required to establish that the oily coats observed in rats fed hydrogenated poly-1-decene were not the result of systemic absorption. It also requested data that clearly demonstrate the lack of absorption of this substance in humans. In the absence of these data, the Committee noted that the results of long-term toxicity and reproductive toxicity studies and information on the metabolism, distribution and excretion of hydrogenated poly-1-decene would be required. The only study submitted to the Committee at its present meeting was an investigation of the distribution and excretion of hydrogenated poly-1-decene and of the origin of the oily coats in rats

in the 90-day study. All relevant data, including those reviewed at the forty-ninth meeting, were evaluated at the present meeting.

[^{3}H]Hydrogenated poly-1-decene (97% radiochemical purity), administered as a single oral dose of 30, 210 or 1500mg/kg of body weight to rats, was eliminated almost entirely in the faeces, with 0.2%, 0.05% and 0.6% of the dose, respectively, excreted in the urine. In rats treated with 210mg/kg of body weight per day for 14 days, 0.07% of the dose was eliminated in the urine. Negligible amounts were detected in the bile of all treated animals. The very low concentrations of radiolabel in plasma and tissues did not increase in direct proportion to the dose, suggesting that absorption was limited at high doses. At 8 hours after dosing, 60–80% of the radiolabel in plasma was present as $[^3H]_2O$ (tritiated water), indicating that the label had a half-life of 80–90 hours. The ratio of the concentration of the radiolabel in the liver or lymph nodes (site unspecified) to that in plasma was approximately 5, which suggested that the material in these tissues was not simply $[^3H]_2O$ and that the material had been absorbed from the gastrointestinal tract through the lymphatic system. The absorbed radiolabel was not characterized further, and the results of administration of an intravenous dose did not provide useful information on the disposition of the parent compound through the circulation. The study indicated very little absorption of hydrogenated poly-1-decene in rats after oral administration but was uninformative with regard to the disposition of the compound. The Committee concluded that the oiliness of the fur observed within 1–6 hours of dosing was associated with radiolabelled material originating from the anal region which was spread by grooming activity.

In the 90-day study, rats of each sex received diets containing hydrogenated poly-1-decene at 1, 7 or 50g/kg of feed; some animals were maintained on a control diet for a 4-week recovery period. Both males and females in the highest-dose group had ungroomed coats during the second week of treatment and then oily coats from the third week of treatment to the first week of the recovery period. Animals in all treatment groups showed hair loss during treatment; this effect persisted in animals in the highest-dose group throughout the recovery period. Some marginal effects on haematological parameters were noted. Males in the highest-dose group showed a significant, but reversible, reduction in liver weight, which was not associated with any unusual histological appearance. Females in the highest-dose group showed no effect on liver weights, but histological examination revealed necrosis of individual hepatocytes and a decrease in the fat content of hepatocytes. In the 28-day study, a dose-related decrease in the weights of mandibular lymph nodes was noted, which reached

statistical significance in females at the highest concentration tested, 50 g/kg of feed, but was not associated with histopathological changes. This parameter was not evaluated in the 90-day study. Accumulation of saturated hydrocarbons was not observed in lymphoid, gastrointestinal, hepatic or splenic tissue.

No genotoxicity studies have been conducted with hydrogenated poly-1-decene; however, the results of genotoxicity tests on related isoparaffins of lower relative molecular mass showed that they had no effect on a variety of end-points. Consequently, the Committee concluded that genotoxicity tests on hydrogenated poly-1-decene were not required.

Patch tests on human skin with the same related isoparaffins did not indicate sensitization.

The Committee noted that the study of the disposition of hydrogenated poly-1-decene did not allow clear definition of the fate or deposition of any absorbed material. It was therefore unable to establish an ADI. Before reviewing this substance again, the Committee would wish to see an adequate study of the absorption and deposition of hydrogenated poly-1-decene in order to determine whether further studies were required.

A toxicological monograph was prepared. The existing specifications were revised, with minor changes.

3.2 Sweetening agent: erythritol

Erythritol is a four-carbon sugar alcohol (*meso*-1,2,3,4-butanetetrol) with a sweetness that is 60–80% that of sucrose. It is intended for use as a low-calorie sweetener. It is manufactured from glucose or sucrose by fermentation with *Trichosporonoides megachiliensis* or *Moniliella pollinis*, which are non-pathogenic, non-toxicogenic yeasts. Erythritol also occurs naturally in fruits and mushrooms and is present in various fermented products, including wine, *sake* and soy sauce, generally at low concentrations (700–1300 mg/kg), but in the exceptional case of a single species of mushroom, at 34 g/kg. It is often detected in human and animal tissues and body fluids, including the lens, cerebrospinal fluid, serum, semen and urine.

Erythritol has not been previously evaluated by the Committee. Its technical characteristics, such as its cooling effect and low hygroscopicity, are more similar to those of xylitol than those of sorbitol, which together account for a large proportion of sweetening agents on the market. If erythritol were to be used to replace xylitol (which accounts for 20% of all polyol use), the projected mean intake would be

1 g/day and the intake in the 90th percentile, based on the estimated intake of diabetic patients, would be 4 g/day; if it were used to replace all polyols, the mean intake would be 4–5 g/day and the intake in the 90th percentile would be 20 g/day.

Studies in mice, rats, dogs and humans showed that erythritol is rapidly and extensively absorbed after oral ingestion and rapidly excreted unchanged in the urine. Excretion in the faeces was a minor route after dietary administration to mice, rats and dogs; no data were available for humans. The small but significant proportion of the administered dose recovered in expired carbon dioxide after oral administration was probably the result of fermentation of erythritol in the lower gastrointestinal tract; the proportion increased in a dose-related manner. In contrast, the major route of excretion of orally administered glycerol, lactitol and mannitol was expired carbon dioxide, negligible amounts being excreted unchanged in the urine and faeces. These findings indicate the importance of gastrointestinal fermentation in the disposition of these polyols. There was no evidence of fermentation of erythritol by the gastrointestinal flora in humans who had not been exposed to it previously.

Erythritol showed little toxicity when administered orally to mice, rats and dogs as a single dose. The symptoms observed in animals that subsequently died were considered to be nonspecific effects resulting from the absorption of a large volume of a hypertonic solution.

Toxicity studies were conducted in mice given erythritol in the diet for 13 weeks, in rats treated for 28 days in the diet (two studies) or for 13 weeks in the diet or by gavage, and in dogs treated by gavage for 13 weeks or in the diet for 1 year. In all of these studies, concentrations of up to 200 g/kg of diet were used. In both male and female rodents, administration of erythritol was accompanied by dose-related increases in water consumption and urine volume. Urine density and osmotic pressure were increased at the lower doses and decreased at the higher doses, reflecting the competing factors of high concentrations of erythritol and its effects on diuresis. Urinary excretion of electrolytes, particularly sodium, potassium and calcium (measured only after dietary administration), and of protein was also increased in rats and mice. Increased kidney weights were observed in rats but not in mice. In the study in which erythritol was administered for 28 days in the diet of rats that had undergone partial nephrectomy, no difference in response was seen between sham-operated and nephrectomized animals. Other effects related to diuresis were seen in response to erythritol only in the 13-week study in rats treated by gavage; these included increased blood urea nitrogen concentration,

decreased serum concentrations of sodium and chloride, an increased incidence of slight dilatation of the renal tubules, and increased adrenal weights accompanied by dilatation of the sinusoids of the adrenal cortex. These effects were no longer seen after a 4-week recovery period. The results of an additional study to investigate these effects suggested that the increase in blood urea nitrogen concentration was a compensatory homeostatic response to serum hyponatraemia. The more extensive effects noted after administration by gavage were probably related to the higher maximum plasma concentrations of erythritol after a bolus dose than after gradual intake in the diet.

Gastrointestinal effects were seen in all of the studies in which erythritol was administered orally. These included transient laxation and soft stools in rats and increased caecal weights in both rats and mice. The decrease in caecal pH in the 13-week study in rats treated in the diet would have promoted increased absorption of calcium and might therefore account for the increased urinary excretion of calcium. Serum alkaline phosphatase activity was increased by treatment in these studies. Since the main source of circulating alkaline phosphatase in rats is the intestine, the increase in plasma activity may have resulted from the intestinal effects of erythritol.

In dogs, transient clinical effects (salivation, vomiting, reddening of the epidermal and mucous membranes, laxation and soft stools) were seen after treatment by gavage but not after dietary administration. These effects, with the exception of that on faecal consistency, were attributed to increased plasma osmolality. As in the rodents, water consumption and urine volume were increased in both studies, with increased osmotic pressure and specific gravity of the urine observed at the lower doses and decreases in these parameters at the higher doses. Renal function, as assessed by clearance of phenosulfonphthalein after treatment by gavage, was not affected. In the 1-year study, some histopathological changes were seen in the kidneys of 2 of the 3 dogs at the highest dose, which regressed during the 4-week recovery period and were considered to be a transient, functional osmotic response. Changes observed in the prostate were considered not to be toxicologically relevant.

All of the effects seen in these short-term studies in rodents and dogs were considered to be physiological or adaptive responses to the osmotic diuretic effects of absorbed erythritol or (in rodents) the effect of gastrointestinal fermentation of unabsorbed erythritol. All of these effects were reversed when feeding of erythritol was stopped. Intravenous administration of erythritol to rats resulted in physiological changes that were qualitatively similar to those observed after

administration in the diet or by gavage but were more marked. The NOEL in the feeding studies was 50 g/kg of feed, equivalent to 7.5 g/kg of body weight per day in the 13-week study in mice, 2.5 g/kg of body weight per day in the 13-week study in rats and 1.7 g/kg of body weight per day in the 1-year study in dogs. The NOELs in the studies in which erythritol was given by gavage for 13 weeks were 2 g/kg of body weight per day in rats and 1.2 g/kg of body weight per day in dogs.

Erythritol was not carcinogenic in rats treated in the diet for 78 or 104 weeks; no long-term toxicity studies in mice were available. Effects similar to those seen in the short-term studies were observed in the rats, with the addition of earlier onset of nephrosis in males at the highest dose. The NOELs for physiological responses to erythritol were 30 g/kg of feed (equal to 1.4 g/kg of body weight per day) in the 78-week study and 20 g/kg of feed (equal to 0.9 g/kg of body weight per day) in the 104-week study.

Erythritol did not exhibit mutagenic or clastogenic activity in vitro.

No reproductive or developmental toxicological effects were observed at doses of up to 8 g/kg of body weight per day in mice given by gavage or at doses representing up to 100 g/kg of feed in rats.

The gastrointestinal and renal effects of erythritol and its effects on glucose control have also been studied in volunteers. When single doses of 30–75 g of erythritol were administered in solution or jelly to healthy adults in three studies, the NOEL for induction of laxation was 0.46–0.66 g/kg of body weight in men and 0.76–0.80 g/kg of body weight in women. The dose that induced laxation in 50% of the subjects was estimated to be 1.1 g/kg of body weight in men and 1.6 g/kg of body weight in women. Although women appeared to be less sensitive to erythritol-induced laxation than men, they reported gastrointestinal symptoms, including nausea, more frequently. When a divided dose of 40 g of erythritol in solution was ingested by healthy individuals daily for 5 days or divided doses of 60–68 g/day were ingested in tea or coffee for 3 days, no laxation occurred at doses of up to 0.91 g/kg of body weight per day in men and 0.74 g/kg of body weight per day in women. Single doses of 0.3 and 1 g/kg of body weight of erythritol in aqueous solution given to healthy adults had no effect on plasma glucose or insulin concentrations, and neither urine volume nor urinary excretion of sodium, chloride or potassium was affected by the lower dose.

No gastrointestinal symptoms were seen when single doses of 0.4 or 0.8 g/kg of body weight were given in food, or when repeated doses of 1 g/kg of body weight per day were ingested in a variety of foods

throughout the day for 5 days by healthy individuals. The osmolality of urine was increased by erythritol treatment in a dose-related manner in both of these studies. After single doses of erythritol, no changes in measured plasma osmolality were observed, and there was no effect on water consumption, urine volume or 24-hour excretion of electrolytes or *N*-acetyl-glucosaminidase. Plasma glucose levels were not affected.

In subjects with non-insulin-dependent diabetes, a 20-g dose of erythritol in solution consumed on a single occasion or on 14 consecutive days did not induce laxation and had no effect on blood glucose concentrations.

The NOELs for physiological responses to orally administered erythritol in animals were generally between 1 and 2 g/kg of body weight per day. Since the observed effects of erythritol in animals are a physiological response to an osmotically active substance, application of a safety factor to the NOELs observed in studies in experimental animals was considered inappropriate. In humans, a dose of 1 g/kg of body weight per day consumed in a variety of foods for 5 days had no effect, although the same (and lower doses) consumed in aqueous solution as a bolus dose after fasting resulted in laxation. The Committee established an ADI "not specified"[1] for erythritol for use as a sweetening agent.

A toxicological monograph and new specifications were prepared.

3.3 Thickening agent: curdlan

Curdlan is a linear polymer consisting of β-(1→3)-linked glucose residues, which is derived by fermentation from the bacterium *Alcaligenes faecalis* var. *myxogenes*. It has not been previously reviewed by the Committee. At its present meeting, the Committee considered use of curdlan in food as a formulation aid, processing aid, stabilizer and thickener or texturizer.

Information on the current per capita intake of curdlan in Japan was submitted, together with intake data based on the levels of use of the additive and on food consumption in the USA. However, the

[1] ADI "not specified" is used to refer to a food substance of very little toxicity which, on the basis of the available data (chemical, biological, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.