Calorie Control Council

5775 Peachtree-Dunwoody Road, Building G, Suite 500
Atlanta, GA 30342
www.caloriecontrol.org
ccc@kellencompany.com
Phone 404-252-3663 Fax 404-252-0774

September 7, 2001

RECEIVED
SEP - 7 2001
CERHR

Mr. Michael Shelby
CERHR Director
NIEHS
76 T.W. Alexander Drive
Building 4401, Room 103
P.O. Box 12233, MD EC-32
Research Triangle Park, NC 277-9
FAX 919-316-4511
shelby@niehs.nih.gov

Dear Dr. Shelby:

RE: Draft Methanol Expert Panel Report

The Calorie Control Council (the "Council") is an international association of manufacturers of low-calorie, reduced-fat and "light" foods and beverages. The Council also represents companies that make the low-calorie ingredients, sweeteners, fat replacers and bulking agents, which make these products possible. Companies that make and use aspartame are among the Council's members. The Council provides the following comments on the National Toxicology Program's Draft "NTP-CERHR Expert Panel Report on Reproductive and Developmental Toxicity of Methanol."

The Council is concerned about the report's strong emphasis on aspartame as a source of methanol. As the Expert Panel notes: "Dietary exposures to methanol are not well characterized with the exception of methanol exposure through the intake of aspartame." There is, however, a substantial amount of information on aspartame demonstrating that the consumption to aspartame is safe and, furthermore, there is no cause for concern related to methanol from the consumption of aspartame. The emphasis that the report in its present form places on aspartame is more likely to cause speculation and concern than relay the fact that there is no concern The accuracy and clarity of the information on aspartame to be provided in the report is especially important in light of the volume of aspartame misinformation on the Internet and the propensity of activists to twist and misinterpret aspartame information.

The Council also is concerned about the aspartame consumption data used in the draft report. The dietary methanol exposures to humans from aspartame, as stated in the draft report, are an overestimation based on obsolete data and hypothetical pre-approval projections of aspartame intake. Estimations of dietary methanol intake from aspartame used in the report should be revised to include actual levels of aspartame intake which have been published in the peer-

reviewed scientific literature, and are well below the hypothetical pre-marketing projections noted in the draft report. The estimated daily consumption of aspartame at the 99th percentile was 34 mg/kg bw/day; the actual 90th percentile aspartame intake is 3 mg/kg bw/day or about 1/10th of the theoretical 99th percentile pre-marketing estimate. (This point is further discussed in section III of the attached comments.)

Information to further elucidate the above and to further support the safety of aspartame is provided below.

I. Introduction

The draft Methanol Expert Panel Report notes the dietary exposure to methanol from fruits and vegetables and their juices, wines, and other alcoholic beverages. In addition, the draft report highlights the sweetener, aspartame (L-aspartyl-L-phenylalanine methyl ester), as representative of oral exposure to methanol because, upon ingestion, it is metabolized to its constituents – the amino acids, aspartate and phenylalanine, and about 10% methanol by weight. A number of comments in the report regarding aspartame should be clarified.

Some major points that must be included in the final report:

- The pre-marketing projections of aspartame intake used in the report are not appropriate. They were based on pre-marketing estimates that aspartame [mean = 8.3 mg/kg body weight (bw)/day] would replace all dietary sugar intake and aspartame would be used in all products based on survey data (34 mg/kg bw/day at the 99th percentile). These projections have proven to be overly conservative in light of the extensive post-marketing aspartame intake data available in the scientific literature.

- Daily aspartame intake by the general population of aspartame consumers in the US has ranged from 1.6 - 3.0 mg/kg bw (90th percentile). This is approximately 1/10th of the amount noted in pre-marketing projections cited in the draft report. The FDA has since determined that the 90th percentile is more indicative of high-level consumption than the 99th percentile formerly used for pre-marketing projections. Thus, methanol intake from aspartame is only about 0.3 mg/kg bw/day.

- Dietary exposure to methanol from fruits and vegetables and their juices and alcoholic beverages makes up a greater percent of total safe dietary methanol intake than do aspartame and another food additive, dimethyl dicarbonate (DMDC).

- The safety of dietary methanol exposure, including from the food additives, aspartame and DMDC, has been evaluated by the Food and Drug Administration (FDA). The FDA has concluded, "...the tolerable (safe) level of exposure to methanol is 7.1 to 8.4 milligrams per kilogram body weight per day (mg/kg body weight/day), or approximately 426 to 504 mg/person/day for a 60 kg adult" (FDA, 1994, 1996a).

II. Safe dietary exposure to methanol provided by fruits and vegetables and their juices, wines, and other alcoholic beverages

As noted in the draft report (page 5, paragraph 4 and Table 7.1-C), safe dietary exposure to methanol from fruits and vegetables and their juices and alcoholic beverages has been the subject of investigation for a number of years with a range of methanol concentrations reported from different studies. In addition, other sources of dietary methanol in a healthy diet included filbert

nuts, legumes, and vegetables not typically used for juices, such as potatoes, onions, Brussels sprouts, celery, and parsnips. Although there appears to be a paucity of published data on the subject, the draft report fails to discuss or elaborate on the potential oral exposure to methanol from these other food sources.

As noted by several authors, the methanol content of juices depends not only on the type of fruit but also on the ripeness of the fruit as well as the type of processing and storage time (Bindler et al, 1988; Kirchner and Miller, 1957; Kirchner et al., 1953), which may account for the range of concentrations reported. In addition, Wucherpfennig et al. (1983) point out that the methanol content of juices should be addressed from the standpoint of "total" methanol content, i.e., "existing" (i.e., "free") methanol in the juice plus the "potential" (i.e., "releasable") methanol that is made available as pectin is broken down by enzymes or during storage or ingestion. For example, in tomato juice the "existing" methanol content of 159 mg/L in addition to "potential" methanol content of 142 mg/L, results in a "total" methanol content of 301 mg/L (Wucherpfennig et al.,1983). In this example, the total methanol exposure is about 2 times the nominal concentration of "free" methanol in tomato juice, which suggests that the methanol concentrations reported in juices in other studies may be conservative underestimates of dietary methanol exposure.

Consistent with the approach of Wucherpfennig and coworkers, a report from a panel of experts published by the World Health Organization (WHO, 1997) noted that dietary methanol can arise from fresh fruits and vegetables as free methanol, methyl esters of fatty acids or methoxy groups on polysaccharides such as pectin. Sommer (1962) and Grüner et al. (1994) have reported that pectins are metabolized in the human GI tract with consequent release and absorption of methanol. Therefore, it is likely that a healthy diet actually safely provides greater amounts of methanol than would appear to be the case from the methanol contents reported in the literature above and summarized in the draft report.

Finally, Taucher et al. (1995) calculated the lower limit of the actual rate of methanol production in humans after eating fruit by evaluating methanol in human breath. These authors estimated "methanol production in the human body of up to ~0.1 g/hr, showing that because of fruit consumption, the body can produce ~1 g of methanol over the time period of 1 day in addition to the background natural (physiological) base methanol production (~0.015 g/hr)." Based on these findings, significant amounts of dietary methanol from fruits are commonly and safely handled by humans.

III. Safe dietary methanol exposure from aspartame

Regarding aspartame, the dietary methanol exposures to humans from aspartame, as stated in the draft report (page 6), are an overestimation based on obsolete data and hypothetical pre-approval projections of aspartame intake (FDA, 1981). Estimations of dietary methanol intake from aspartame should be revised to include actual levels of aspartame intake, which have been published, and are well below the hypothetical pre-marketing projections used in the draft report (Butchko and Kotsonis, 1991, 1994, 1996; Butchko et al., 1994; Butchko and Stargel, in press 2001).

Before approving a food additive, regulatory agencies, including the FDA and agencies in other countries, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) require extensive documentation of a food additive's safety for its intended uses. This typically includes data from two 2-year carcinogenicity studies (one in rats including *in utero* exposure and the other in mice), chronic 1-year toxicity studies in two species, as well as reproduction, teratology,

and mutagenicity studies at doses greatly exceeding anticipated human intakes. Based on the results of these studies, regulatory agencies such as FDA determine a no-observed-effect-level (NOEL) for the additive. The Acceptable Daily Intake (ADI), the amount (in mg/kg bw/day) that would be considered safe if consumed everyday for a lifetime, is typically set as 1/100th of the NOEL. At times, data from humans, when available, may also be used to determine the ADI. As part of the approval process, FDA and regulatory agencies in other countries also evaluate potential human exposure to the additive relative to the ADI to determine the level of use that is permitted to assure that intake does not exceed the ADI on a consistent basis.

In the case of aspartame, all of these preclinical studies as well as others, including a number of human studies, have been evaluated by regulatory agencies around the world. The doses of aspartame in the animal studies were hundreds of times greater than the estimated human exposure (see page 6 in the draft report for pre-marketing exposure estimates). Aspartame is rapidly metabolized in the gastrointestinal tract to its components – the amino acids, aspartic acid and phenylalanine, and 10% methanol by weight. Thus, the impact of these three components on their blood concentrations was also evaluated in these studies. FDA concluded that the amount of aspartame and its components to which humans would be exposed from its intended use as a sweetener and flavor enhancer is safe (FDA 1981, 1983, 1984).

As the draft report states on page 6, it is true that, prior to approval, mean projected intake of aspartame in the United States was projected to be 8.3 mg/kg bw/day if all sucrose in an average-sized (60 kg) person's diet was replaced by aspartame. It is also true that other pre-marketing projections of aspartame exposure were based on evaluation of 2-week dietary records from close to 12,000 individuals. From these data, FDA estimated that, if all possible sweetened foods and beverages were replaced with aspartame-containing foods and beverages, the 99th percentile daily consumption of aspartame would be 34 mg/kg bw (FDA, 1981). Since then, FDA has determined the 90th percentile to be more indicative of high-level exposures (FDA, 1986). Thus, in the case of aspartame, actual 90th percentile intake is 3 mg/kg bw/day or about 1/10th of the theoretical 99th percentile pre-marketing estimate. This 90th percentile value should be used to evaluate methanol exposure from aspartame in the draft report.

Aspartame intake has been most extensively evaluated in the US. MRCA collected detailed data on aspartame intake by means of their menu census surveys from over 2,000 households a year from 1984 -1992 (Butchko and Kotsonis, 1991, 1994, 1996; Butchko et al., 1994; Butchko and Stargel, in press 2001). The approximately 5,000 people surveyed per year were a valid, representative sample of the general U.S. population. Aspartame intake at the mean and various percentiles (50th, 90th, 95th, and 99th) were tabulated as averages over 14 days, both for "eaters," who consumed aspartame at least once during the survey, and the population at large.

Because of their smaller body weights, children may consume more of an additive on a mg/kg bw/day basis than adults. To evaluate intake by children specifically, data also were recorded by specific age group: 0-23 months, 2-5 years, 6-12 years, 13-17 years, 18 years and over, as well as all age groups together. In addition, intake was also monitored for special population subgroups such as diabetics and people on weight-reduction programs, who might be enthusiastic users of aspartame with potentially higher intakes, and women of childbearing potential. In some years, intake by pregnant women was also calculated.

These data established that the 90th percentile 14-day average daily aspartame intake for individuals who consume aspartame ("eaters") in the general population ranged from 1.6 to 3.0 mg/kg bw/day. As shown in Table 1, 90th percentile intake of aspartame, even by children, diabetics, people on weight-reduction diets, females of childbearing age, and pregnant women

was only approximately 5 - 10% of the ADI for aspartame of 50 mg/kg bw/day in the United States.

Table 1. Aspartame intake (mg/kg bw/day) in the United States: 90th percentile, 14-day average, "eaters" only

Survey dates	7/84-6/85	7/85-6/86	7/86-6/87	7/87-6/88	7/88-6/89	7/89-6/90	7/90-6/91	7/91-6/92
Population								
All ages	1.6	2.1	2.1	2.3	2.2	2.5	2.8	3.0
2-5 years	3.1	4.8	3.7	2.6	4.0	3.1	3.5	5.2
Diabetics	2.1	2.2	3.0	3.3	2.6	2.7	3.4	3.3
Reducing diet	1.6	2.2	2.3	2.6	2.5	2.7	2.8	3.3
Childbearing age	2.0	2.2	2.5	2.8	2.6	3.2	3.7	4.2
Pregnant females	2.4	1.3	1.7	2.7	--	--	--	--

Further, although methodologies differed among countries, the results of surveys from ten other countries (UK, Germany, France, Finland, Italy, Canada, Norway, Netherlands, Australia, and Brazil) have also found intake levels of aspartame to be consistent with data from the U.S (Hinson and Nicol, 1992; MAFF, 1990, 1995; Bar and Biermann, 1992; Chambolle et al., 1994; Garnier-Sagne et al, 2001; Virtanen et al., 1988; Leclercq et al, 1999; Heybach and Ross, 1989; Bergsten, 1993; Hulshof and Bouman, 1995; National Food Authority Australia, 1995; Toledo and Ioshi, 1995). For example, 90th percentile daily intake of aspartame was 1.6 mg/kg bw in the UK, 2.8 mg/kg bw in Germany, 5.9 mg/kg bw in Canada, and 0.6 mg/kg bw in France.

Thus, basing oral methanol exposure from aspartame on pre-marketing projections of intake is not appropriate; actual 90th percentile consumption data for aspartame from the general population is about an order of magnitude less than the pre-marketing estimate (99th percentile) of 34 mg/kg bw/day cited in the draft report. Thus, as aspartame is 10% methanol by weight, the 90th percentile daily intake of methanol from aspartame is only 0.3 mg/kg bw/day for the US general population or about 18 mg/day for a 60 kg adult.

IV. FDA has evaluated the safety of dietary methanol ingestion

FDA (1983, 1984) specifically evaluated the potential impact of aspartame on dietary intake of methanol at the time of approval and found no cause for concern even at the highest projected intake levels. In addition, FDA has since approved another food additive, DMDC (a yeast inhibitor in ready-to-drink tea beverages, sports drinks, fruit or juice sparklers, wines, and wine substitutes) (FDA, 1988, 1994, 1996a), which also adds methanol to the diet.

In its evaluation of all current uses of DMDC, FDA (1996) concluded that intakes of methanol from untreated fruit juices and wine in the diet was 25 mg/person/day at the mean and 48 mg/person/day at the 90th percentile of consumption. With the addition of DMDC to the dietary uses described above, methanol intake was projected to be 30 mg/person/day at the mean and 59 mg/person/day at the 90th percentile.

Using actual aspartame intake data of 3.0 mg/kg/day (90th percentile), which amounts to 180 mg/person/day for 60 kg person, aspartame contributes only 18 mg of methanol at the 90th percentile. Thus, dietary methanol exposure from fruit juices and wines plus these two food additives at the 90th percentile of intake is about 77 mg/person/day or 1.3 mg/kg bw/day for a 60 kg individual.

Thus, contrary to the statement in the draft report (page 7), that fruits and vegetables in the diet do not provide equivalent or greater amounts of methanol compared to aspartame, based on FDA's estimates of dietary methanol exposure, the normal diet provides far greater amounts of methanol than does aspartame (i.e., 48 mg/person/day from untreated fruit juices and wine compared to 18 mg/person/day from aspartame).

Further, FDA has also considered metabolic capacity when evaluating safe levels of methanol intake in humans. FDA (1988) stated, "An adult human can metabolize up to 1500 milligrams of methanol per hour with no adverse symptoms or effects." Thus, the capacity for methanol metabolism in humans is far greater than estimated dietary intake.

In evaluating dietary methanol exposure in the approvals of DMDC, FDA (1994, 1996a) concluded, "...the tolerable (safe) level of exposure to methanol is 7.1 to 8.4 milligrams per kilogram body weight per day (mg/kg body weight/day), or approximately 426 to 504 mg/person/day for a 60 kg adult." Thus, there is a large margin of safety between actual dietary intake of methanol and the amount that can be safely ingested.

V. Additional safety evaluations regarding methanol derived from aspartame

In addition to the few studies cited in the draft report from Stegink and coworkers on acute exposure to methanol from aspartame, there are many other human studies of aspartame's safety, which should be taken into account. Many of the numerous publications on aspartame are discussed and referenced in two books (Stegink and Filer, 1984; Tschanz et al., 1996).

A human study by Leon et al. (1989) is particularly relevant because of the very high doses of aspartame given over a long period of time. In this study, healthy adult subjects were given 75 mg/kg bw of aspartame or placebo daily for 6 months (i.e., about 25 times the 90th percentile average daily intake of aspartame by the general population or the amount of aspartame in about 25 12-ounce cans of beverage sweetened with aspartame for a 60 kg person). This very large dose of aspartame provides 7.5 mg/kg bw/day of methanol. During the study, most blood methanol concentrations were below the limit of detection (0.31 mmol/L) in both the aspartame and placebo groups. The number of subjects with detectable blood methanol concentrations was similar in both groups. Thus, there was no accumulation of methanol from long-term ingestion of these very large doses of aspartame. In addition, blood formate concentrations were not significantly increased after aspartame. Further, evaluation of 24-hour urine collections revealed no increased urinary formate excretion after aspartame compared to placebo or in urinary formate to creatinine ratio, indicating no significant increase in formate formation during high dose, long term aspartame use.

In addition, since the draft report highlights aspartame as a source of methanol, it is important that the complete database of safety studies with aspartame be considered. In compliance with US and international regulatory requirements, the safety of aspartame – and thus also its metabolic components – was extensively evaluated before approval (JECFA, 1980; Kotsonis and Hjelle, 1996). The preclinical toxicology studies included four 2-year or lifetime studies in rodents, including one in rats with *in utero* exposure followed by 104 weeks of testing, as well as reproduction and teratology studies in rats and rabbits. The no-observed-effect dose of aspartame was at least 4,000 mg/kg bw/day, providing up to 400 mg/kg bw/day of methanol. This dose is the equivalent of a 60 kg human consuming 24,000 mg of methanol every day. There were no adverse effects, including no carcinogenicity and no reproductive, developmental or teratogenic effects with these enormous doses of aspartame and methanol.

VI. Other comments:

Page 67, Line 1

The statement "...2.5-2.7 mg/kg/day or phenylalanine at 1.65 mg/kg/day..." should be corrected to "...2.5-2.7 **g**/kg/day or phenylalanine at 1.65 **g**/kg/day..."

Table 7.1-C. Methanol Levels in Foods and Beverages

A correction in the table is needed: Under Fresh and canned fruit juices, the correct reference is #1 for the level 12-640 mg/L not #2 as stated.

As a note, there is inconsistency in referencing the methanol in foods and beverages data; in some cases, the original reference is cited (e.g., Greizerstein, #16 and Lund et al., #121) whereas in most cases, the secondary literature (#1 – the WHO report) is cited.

VII. Conclusions:

- Based on differences in ripeness and processing of fruit juices reported in the literature and the ability of humans to metabolize pectin, it is likely that a normal diet safely provides greater amounts of methanol than would appear to be the case from the methanol contents of juices reported in the literature.

- The pre-marketing projections of aspartame intake used in the report were based on estimates of aspartame (mean = 8.3 mg/kg bw/day) to replace all daily dietary sugar intake and the use of aspartame in all possible products based on survey data (34 mg/kg bw/day at the 99th percentile). These projections were shown to be inappropriate in light of the extensive post-marketing aspartame intake data readily available in the scientific literature.

- Daily aspartame intake by the general population of aspartame consumers in the US has ranged from 1.6 - 3.0 mg/kg bw (90th percentile) or about 1/10th of the pre-marketing projections cited in the draft report. (In contrast to the 99th percentile pre-marketing projections, the FDA has subsequently determined the 90th percentile to be more indicative of high-level consumption). Thus, aspartame provides only about 0.3 mg/kg bw of methanol to the daily diet.

- Dietary exposure to methanol from fruits and vegetables and their juices and alcoholic beverages makes up a far greater percent of total dietary methanol exposure than does aspartame and another food additive, dimethyl dicarbonate (DMDC).

- Based on FDA's estimates of dietary methanol exposure, the normal diet safely provides greater amounts of methanol than does aspartame (i.e., 48 mg/person/day from untreated fruit juices and wine compared to 11 and 18 mg/person/day from DMDC and aspartame, respectively).

- Regarding the safety of dietary methanol exposure, FDA has concluded, "... the tolerable (safe) level of exposure to methanol is 7.1 to 8.4 milligrams per kilogram body weight per day (mg/kg body weight/day), or approximately 426 to 504 mg/person/day for a 60 kg adult" (FDA, 1994, 1996a).

- According to the FDA (1988), "An adult human can metabolize up to 1500 milligrams of methanol per hour with no adverse symptoms or effects." Thus, the capacity for methanol metabolism in humans is far greater than the estimated dietary intake.

- In addition to the few human studies cited in the draft report from Stegink and coworkers on acute exposure to methanol from aspartame, there are many other studies with aspartame in humans, which should be taken into account from a safety standpoint.

- The no-observed-effect level dose of aspartame derived from animal carcinogenicity (four 2-year or lifetime studies, one with *in utero* exposure), reproductive, and teratology studies was at least 4,000 mg/kg bw/day, providing up to 400 mg/kg bw/day of methanol. This dose is the equivalent of a 60 kg human consuming 24,000 mg of methanol every day. There were no adverse effects, including no carcinogenicity and no reproductive, developmental or teratogenic effects of these enormous doses of aspartame and methanol.

We trust these comments will be carefully considered. A list of references is attached (Attachment A). References are available upon request.

Respectfully submitted,

Lyn O'Brien Nabors

Lyn O'Brien Nabors
Executive Vice President

Attachment

ATTACHMENT A

REFERENCES

Bar, A., and Biermann, C. (1992). Intake of intense sweeteners in Germany. *Z. Ernahrungswiss.* **31**, 25-39.

Bergsten, C. (1993). *Intake of acesulfame-K, aspartame, cyclamate and saccharin in Norway.* SNT Report **3**. Norwegian Food Control Authority, Oslo, Norway.

Bindler, F., Voges, E., and Laugel, P. (1988). The problem of methanol concentration admissible in distilled fruit spirits. *Food Addit Contam.* **5**, 343-351.

Butchko, H. H., and Kotsonis, F. N. (1991). Acceptable daily intake vs actual intake: the aspartame example. *J. Am. Coll. Nutr.* **10**, 258-266.

Butchko, H. H., and Kotsonis, F. N. (1994). Postmarketing surveillance in the food industry: the aspartame case study. In *Nutritional Toxicology* (F. N. Kotsonis, M. Mackey, and J. Hjelle,. Eds.), pp. 235-250. Raven Press, New York.

Butchko, H. H., and Kotsonis, F. N. (1996). Acceptable daily intake and estimation of consumption. In *The Clinical Evaluation of A Food Additive: Assessment of Aspartame.* (C. Tschanz, H. H. Butchko, W. W. Stargel, and F. N. Kotsonis,. Eds.), pp. 43-53. CRC Press, Boca Raton.

Butchko, H. H., Tschanz, C., and Kotsonis, F. N. (1994). Postmarketing surveillance of food additives. *Regul. Toxicol. Pharmacol.* **20**, 105-118.

Butchko, H. H. and Stargel, W.W. (2001). Aspartame: Scientific evaluation in the postmarketing period. *Regul. Toxicol. Pharmacol.* In press.

Chambolle, M., Collerie de Borely, A., Renault, C., and Volatier, J. (1994). Intake of intense sweeteners in France (1989-1992). CREDOC, Departement Prospective de la Consommation, Paris.

FDA. (1981). Aspartame: commissioner's final decision. *Fed. Regist.* **46**, 38285-38308. July 24, 1981.

FDA. (1983). Food additives permitted for human consumption; aspartame. *Fed. Regist.* **48**, 31376-31382. July 8, 1983

FDA. (1984). Food additives permitted for human consumption; aspartame. *Fed. Regist.* **49**, 6672-6682. February 22, 1984.

FDA. (1986). Food additives permitted for human consumption; aspartame. *Fed. Regist.* **51**, 42999-43000. November 28, 1986.

FDA. (1988). Direct food additives; food additives permitted for direct addition to food for human consumption; dimethyl dicarbonate. *Fed. Regist.* **53**, 41325-41329. October 21, 1988.

FDA (1994). Food additives permitted for direct addition to food for human consumption; dimethyl dicarbonate. *Fed. Regist.* **59**, 5317-5320. February 4, 1994.

FDA. (1996). Memorandum from Chemistry Review Branch (Michael DiNovi) to Direct Additives Branch (M. Peiperi). FAP 4A4420: Miles, Inc. Dimethyl dicarbonate (DMDC) as a yeast inhibitor in "sports drinks" and sparkling fruit of juice beverages. Background methanol exposure. May 8, 1996.

FDA. (1996a). Food additives permitted for direct addition to food for human consumption; dimethyl dicarbonate. *Fed. Regist.* **61**, 26786-26788. May 29, 1996.

Garnier-Sagne, I., Leblanc, J. C., and Verger, P. (2001). Calculation of the intake of three intense sweeteners in young insulin-dependent diabetics. *Food Chem. Toxicol.* **39**, 745-749.

Grüner, O., Bilzer, N., Liebmann, J. (1994). Zur methanolbildung in vitro und in vivo. *Blutalkohol.* **31**, 228-232.

Heybach, J., and Ross, C. (1989). Aspartame consumption in a representative sample of Canadians. *J. Can. Diet. Assoc.* **50**, 166-170.

Hinson, A. L., and Nicol, W. M. (1992). Monitoring sweetener consumption in Great Britain. *Food Addit. Contam.* **9**, 669-680.

Hulshof, K. F. A. M., and Bouman, M. (1995). Use of various types of sweeteners in different population groups. *1992 Dutch National Food Consumption Survey.* TNO Nutrition and Food Research Institute, Netherlands.

Joint Food and Agriculture Organization /World Health Organization Expert Committee on Food Additives (JECFA). (1980). *Toxicological evaluation of certain food additives.* (WHO Tech Rep Ser No. 653). 18-86. Geneva: WHO.

Kirchner. J.G. and Miller, J.M. (1957). Volatile water-soluble and oil constituents of Valencia orange juice. *Agric. Food Chem.* **5**, 282-291.

Kirchner, J. G., Miller, J. M, Rice, R. G., Keller, G. J., and Fox, M. M. (1953). Volatile water-soluble constituents of grapefruit juice. *Agri.c Food Chem.* **1**, 510-518.

Kotsonis, F.N and Hjelle, J.J. (1996). The safety assessment of aspartame: scientific and regulatory considerations. In *The Clinical Evaluation of A Food Additive: Assessment of Aspartame.* (C. Tschanz, H. H. Butchko, W. W. Stargel, and F. N. Kotsonis,. Eds.), pp. 23-41. CRC Press, Boca Raton.

Leclercq, C., Berardi, D., Sorbillo, M. R., and Lambe, J. (1999). Intake of saccharin, aspartame, acesulfame K and cyclamate in Italian teenagers: present levels and projections. *Food Addit. Contam.* **16**, 99-109.

Leon, A. S., Hunninghake, D. B., Bell, C., Rassin, D. K., and Tephly, T. R. (1989). Safety of long-term large doses of aspartame. *Arch. Intern. Med.* **149**, 2318-2324.

MAFF. (1990). Intakes of intense and bulk sweeteners in the UK 1987-1988. *Food Surveillance Paper No. 29.* Ministry of Agriculture, Fisheries and Food, London, UK.

MAFF. (1995). Survey of the intake of sweeteners by diabetics. *Food Surveillance Info. Sheet.* Ministry of Agriculture, Fisheries and Food, Food Safety Directorate. London, UK.

National Food Authority Australia. (1995). *Survey of Intense Sweetener Consumption in Australia: Final Report.* National Food Authority, Canberra, Australia.

Sommer, H. (1962). The physiological fate of methylalcohol released from pectin. *Industrielle Obst. Gemesverwesting.* **47**, 172-173.

Stegink, L. D., and Filer, L. J., Eds. (1984). *Aspartame: Physiology and Biochemistry.* Marcel Dekker, New York.

Taucher, J., Lagg, A., Hansel, A., Vogel, W., Lindinger, W. (1995) Methanol in human breath. *Alcohol. Clin. Exp. Res.* **19**, 1147-1150.

Tschanz, C., Butchko, H. H., Stargel, W. W., and Kotsonis, F. N.,. Eds. (1996). *The Clinical Evaluation of A Food Additive: Assessment of Aspartame.* CRC Press, Boca Raton.

Toledo, M. C. F., and Ioshi, S. H. (1995). Potential intake of intense sweeteners in Brazil. *Food Addit. Contam.* **12**, 799-808.

Virtanen, S. M., Rasanen, L., Paganus, A., Varo, P., and Akerblom, H. K. (1988). Intake of sugars and artificial sweeteners by adolescent diabetics. *Nutr. Rep. Int.* **38**, 1211-1218.

World Health Organization. (1997). Environmental Health Criteria 196: Methanol. Geneva.

Wucherpfennig, K., Dietrich, H., and Bechtel, J. (1983). Vorhandener, gesamter, und potentieller methylalkoholgehalt von fruchtsaften. *Flussiges Obst.* **8**, 348-354, 367-369.