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Preclinical Studies of Aspartame in Nonprimate Animals

Samuel V. Molinary
PepsiCo, Inc., Valhalla, New York

INTRODUCTION

Aspartame, [3-amino-N-(2-carboxyphenethyl)succinamic acid methyl ester], the methyl ester of L-aspartyl-L-phenylalanine, and its principal decomposition product, 3-carboxymethyl-6-benzyl-2,5-diketopiperazine (diketopiperazine, or DKP) have been extensively studied for their toxicological potential for the past 15 years. Over 112 studies concerning the metabolism, pharmacology, and toxicology of these two compounds were filed by G. D. Searle & Company with the Food and Drug Administration (FDA) as proof of the safety of aspartame (APM) as a food additive.* In approving APM as a sweetener in 1981, Commissioner Hayes said (1), "The safety evaluation of aspartame has been a long and arduous process, spanning the tenure of several FDA commissioners. Few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety." While APM may not be the most studied food additive, it probably has had the largest number of studies carried out *prior to* FDA approval.

Of these 112 safety studies submitted to the FDA, 93 are or pertain to reports of studies of aspartame and its DKP in animals. Many of these studies

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These studies are contained in the so-called "E-File" at the Food and Drug Administration, Hearing Clerk File, Administrative Record, Aspartame 75F-0355, Rockville, Maryland.

have been reviewed and evaluated by the Joint Expert Committee on Food Additives (JEC/FA) of the Food and Agricultural Organization of the United Nations and the World Health Organization (FAO/WHO) in 1975, 1976, 1977, and 1980. A monograph on the toxicological evaluation was written following the 1980 JEC/FA meeting in Rome (2). This review will be confined to those animal studies carried out early in the development of aspartame (1968-1974). Some of these studies, especially the carcinogenicity studies in the rat, became the focal point for questions that were considered by the Public Board of Inquiry in 1980; the interpretation of these is discussed in depth elsewhere in this book (3-5).

In proposing a novel compound as a food additive, especially a sweetener which will be consumed by all segments of the population, it is important that the sponsor prove that this compound is safe to a reasonable certainty. The development of a data base for product safety assessment typically starts in three scientific areas: metabolism (including absorption, tissue distribution, pharmacokinetics, and elimination), pharmacology, and toxicology. Metabolism studies are carried out in a number of different species, ultimately including man, and the data obtained are used to design and interpret studies in the other two areas. In this specific case pharmacology studies are performed to discover if the compound has any biological activity other than that of creating the perception of a sweet taste. Pharmacological activity is not a desirable property for a food additive. Toxicology studies are carried out in two parts, acute and chronic exposure, and are undertaken to determine what harm may accrue as a result of ingesting the food additive, especially under conditions of high intake. Each of these areas will be considered as they relate to the studies of animals administered aspartame or its DKP.

The metabolism of aspartame and its diketopiperazine have been extensively studied in mice, rats, rabbits, dogs, monkeys, and man (2,6-19). The major point to emerge from the metabolism studies is that in all species tested, aspartame is broken down in the gastrointestinal tract to its constitutents L-phenylalanine, L-aspartic acid, and methanol. These findings suggest that outside the gastrointestinal tract, any toxicological activity of aspartame would result from systemic imbalances caused by increases in the plasma concentration of these two amino acids and methanol. This finding also suggests that if the dipeptide (aspartyl-phenylalanine) per se had any pharmacological activity, it would be in the gastrointestinal tract itself. This was considered possible since the dipeptide sequence aspartyl-phenylalanine is found at the carboxy terminal end of the gastrointestinal hormones gastrin and cholecystokinin (20).

Studies were undertaken by Bianchi et al. (21) to delineate any pharmacological effects that aspartame might have on the gastrointestinal system. Rats were given 200 mg/kg body weight of aspartame intragastrically and observed for effects on appetite suppression, inhibition or stimulation of gastric secretion, acid secretion, and proteolytic activity. No compound-related effects were observed.

In addition to tests on the gastrointestinal system, other pharmacological tests were carried out in a variety of in vivo and in vitro model systems (22). As pointed out by Potts et al. (23), "some of these studies were done to test specific hypotheses. . .while others. . .were done simply in the interest of safety." An evaluation of central nervous system effects (22,23) in rats fed a diet providing aspartame at 9% (11 g/kg body weight per day) sought to compare high-dose effects of phenylalanine with high doses of aspartame on learning in the rat. These authors concluded that on a mole-for-mole basis, there was no difference between aspartame and L-phenylalanine on the learning behavior of rats. No attempt was made in this study to measure the serum phenylalanine or tyrosine levels.

Possible effects of aspartame ingestion on the cardiovascular system were also studied (22); no pharmacological activity was observed. Aspartame was also tested in mice, rats, and rabbits for endocrine-like activity (24,25): None was found. In all, Searle studied the pharmacological activity of aspartame in 32 different animal studies, all with essentially negative results (22,24,26).

• Toxicology studies were conducted on both aspartame and its DKP in a variety of species for various durations of exposure. These tests are typically done in a sequential fashion, with the data from each study being used to design the next experiment. The usual study sequence is

1. Acute toxicity (LD_{50})
2. Chronic toxicity, short-term (90-day study)
3. Chronic toxicity, long-term (52-week study)
4. Carcinogenicity (104 weeks study)

In addition, a series of teratology and reproduction studies are carried out concurrently with the chronic toxicity studies, as are mutagenicity and other special studies. Since the toxicology-teratology studies carried out on aspartame and its DKP are essentially negative and are too numerous to review in detail, only a few selected studies will be discussed.

Acute toxicity studies were carried out on aspartame and its DKP to establish the concentration that is lethal to 50% of the test animals (LD_{50}). Three species were studied: mice, rats, and rabbits (27,28). The compounds were administered by several routes, with the oral route being most pertinent to food additive safety evaluation. When administered orally at doses up to 5 g/kg body weight, no deaths occurred in any animal, nor was any abnormal behavior noted with either aspartame or its DKP. Therefore the minimum lethal dose for these three species is greater than 5000 mg/kg body weight.

Chronic short-term toxicity studies, 39-90 days in duration, were carried out in mice and rats with aspartame (26,29-31) and with aspartame's DKP (32-34) and in dogs with aspartame (35). No treatment-related or consistent dose-related effects were observed in any of these studies, other than a decrease in body weight at the highest dose, 10 g/kg body weight per day (30). Hematology,

urinanalysis, organ weights, and gross and microscopic pathology were reported to be unremarkable in all studies. The principal purpose of these studies was to establish the dose ranges to be used in the chronic long-term and carcinogenicity studies.

CHRONIC TOXICITY STUDIES OF ASPARTAME

Chronic long-term toxicity studies of aspartame, 52-110 weeks in duration, were carried out in mice (36), rats (37-40), hamsters (41-43), and dogs (44). The study design and findings of these studies are detailed below. In addition, Ishii et al. have studied aspartame and aspartame-DKP mixtures fed to Wistar rats for 104 weeks (3,45). Studies E-33/34 (37,38) and E-70 (40) are also discussed elsewhere in this volume (3-5) with respect to the brain tumor issue.

Mouse

Study E-75 (36) was one of 12 Searle safety studies validated by Universities Associated for Research and Education in Pathology, Inc. prior to the Public Board of Inquiry on Aspartame* (46). This was a 110-week study. Groups of 36 male and 36 female mice (72 mice per dose group) were fed aspartame at 1, 2, and 4 g/kg body weight per day as a diet admix for 110 weeks. A group of 72 males and 72 females served as controls. Mean body weights of treated animals were comparable to those of the control group, even though food consumption was observed to decrease with increased aspartame dosage. During the 110 weeks on test, there were no observed effects on the survival, appearance, or behavior of the test animals. Ophthalmological findings were not remarkable. Although there were sporadic incidences of statistically significant differences in some of the measured hematological and clinical chemistry variables, there were no overall compound- or dose-related effects attributable to aspartame administration. Gross and microscopic pathology studies following necropsy gave no indication of tumorigenic or nontumorigenic changes with respect to aspartame administration.

Rat

In study E-33/34 (37,38) (see also Refs. 39 and 46) groups of 40 male and 40 female rats (80 rats per dose group) were given aspartame at 1, 2, 4, or 8 g/kg body weight per day as a diet admix for 104 weeks. A group of 60 males and 60 females served as controls. For the 104-week duration of the study, there was a slight reduction in mean body weight and in mean food consumption in the

*A detailed history of aspartame's course through the regulatory process in the U.S. is detailed in Ref. 1.

4 g/kg body weight per day dose group; these variables were markedly decreased in animals fed aspartame at 8 g/kg body weight per day. No effects on growth or food consumption were reported at the lower two doses. The 2-year survival for *all* groups was poor, especially the male control group. The investigators attribute the decreased survival to spontaneous disease. Females in the 4 and 8 g/kg body weight per day groups had a survival of only 54% of females in the control group. With the exception of persistent and increased numbers of red and white blood cells in the urine of animals in the 8 g/kg body weight per day group, no treatment-related effects were reported on hematological and clinical chemistry parameters. The authors report that no gross or microscopic pathology findings were treatment related. Brain tumor findings in these animals are discussed elsewhere (4,5).

In addition, Searle conducted a two-generation long-term toxicity study of aspartame (39,40). For this study, groups of 40 male and 40 female rats received aspartame at 2 and 4 g/kg body weight per day as a diet admix for 104 weeks. A group of 60 male and 60 female rats served as controls. All test animals were randomly retested from the F_1 litters of a multigeneration study in which the P_1 animals had been exposed to the corresponding dietary aspartame levels for 60 days prior to mating. The P_1 females were kept on diet during gestation and lactation. For the duration of the study, no treatment-related effects were reported with respect to the survival, behavior, or appearance of the animals. Decreased weight gain and food consumption were reported for the animals fed aspartame at 4 g/kg body weight per day. There was no clear dose- or treatment-related differences, that is, heart-to-body weight ratios were significantly decreased in treated males and liver weight was increased in all treated females. A detailed histopathology review of the brains, livers, and pituitary glands of control and treated rats was done. The types and numbers of neoplasms were comparable between the control and treated groups (see Refs. 4 and 5). An increased incidence of hyperplastic nodules was noted in the livers of treated females; however, it was concluded that these hyperplastic nodules were nonneoplastic and not treatment related.

Hamster

A long-term chronic toxicity study of aspartame in hamsters was started (41, see also Refs. 42 and 43). In this study, groups of five male and five female hamsters were fed aspartame in the diet at 1, 2, 4, and 12 g/kg body weight per day. Groups of 10 male and 10 female hamsters served as controls. All groups were replicated seven times. Erratic decreases in body weights and food consumption were noted early in the study. This was followed by the presence of an unidentified infection (later thought to be "wet tail") in the entire colony. This led to a greater than 50% mortality and subsequent termination of this study at 46 weeks.

Dog

Groups of five male and five female beagle dogs were fed 0, 1, 2, and 4 g/kg body weight per day of aspartame in the diet for 106 weeks (44). Depressed weight gain was reported at all levels of aspartame ingestion. A statistically significant lowering of the hemoglobin, hematocrit, and total red blood cell count was reported in the high-dose male animals. No other consistent effects were noted in the hematology studies. Bromsulfophthalein (BSP) clearance time was increased in the males fed aspartame at 2 and 4 g/kg body weight per day at 78 and 116 weeks. Other liver function tests were not remarkable. Gross and histopathological examination did not reveal any treatment-related effects.

Monkey

Infant monkeys fed large doses of aspartame or phenylalanine for the first 9 months of life were also studied. These data are reviewed by Reynolds et al. in Chap. 20 (19). Neuropathology studies in infant primates administered aspartame (2 g/kg body weight) or aspartame (2 g/kg body weight) plus monosodium L-glutamate (1 g/kg body weight) were negative (17,18).

CHRONIC TOXICITY STUDIES OF DKP

The principal decomposition product of aspartame, its DKP, was studied independently in chronic, long-term toxicity studies in the mouse (47) and rat (48,49).

Mouse

In study E-76 (47), groups of 36 male and 36 female mice were given 0.25, 0.5, and 1 g/kg body weight per day of DKP as a diet admix for 110 weeks. A group of 72 male and 72 female mice served as controls. No treatment-related effects on weight gain, food consumption, appearance, behavior, or survival were reported. No adverse effects were reported for the hematology and clinical chemistry measurements. The only suggestion of a treatment effect in the pathology report was a significant increase in thyroid weight and in the ratio of thyroid to body weight. There were no other tumorigenic or nontumorigenic changes reported that were attributable to administration of aspartame's DKP.

Rat

In this study (48,49), groups of six male and six female rats were fed 0.75, 1.5, and 3 g/kg body weight per day of DKP in the diet for 115 weeks. A group of 12 males and 12 females served as the control. Each group was replicated six times (36 rats per gender per group). No effects were reported with respect to survival, behavior, or appearance; however, animals of both sexes in the 1.5 and

3 g/kg body weight per day groups were shown to have a dose-related, statistically significant increase in food consumption in the high-dose group males. Hematology and clinical chemistry measurements reportedly show no difference from controls. Gross and microscopic pathology studies did not indicate the presence of tumorigenic or nontumorigenic changes related to DKP ingestion.

In addition to these routine chronic toxicity studies, both aspartame and its DKP were studied for specific tumorigenic potential in the urinary bladders of mice (50,51). The same study design was used for each compound. Groups of 200 albino mice (60-90 days of age) had pellets (80% cholesterol and 20% aspartame or 80% cholesterol and 20% DKP) surgically implanted in their urinary bladders. The negative control group animals were implanted with pellets composed of cholesterol and the 8-methyl ether of xanthurenic acid. Each study was 56 weeks in duration, during which time the following parameters were measured or noted: morbidity, mortality, motor and behavioral activity, growth, general external features, and digital palpation of protruding tissue masses. At the termination of the study, all animals were necropsied and examined histopathologically for bladder tumors. Any animals dying during the study were examined in the same way. In neither study was there an increased incidence of bladder tumors over that of the negative controls. These data are discussed in detail by Bryan in Chap. 16 (52).

In addition to studies of toxicity and carcinogenicity, aspartame and its DKP were tested for any effects they might exert with respect to reproduction, reproductive performance, and teratology. For purposes of safety evaluation, these studies are typically done in segments. These segments and their purposes were as follows:

Segment I. To evaluate effects of the test substance on fertility, conception, and implantation. These studies also provide an overview of fetal development and growth.

Segment II. To evaluate the test compound for any embryotoxic and teratogenic effects occurring during the first half of pregnancy.

Segment III. To evaluate the test compound for effects on late pregnancy, parturition, and lactation.

Multigeneration. To evaluate the test compound with respect to the total reproductive performance of two consecutive generations. This includes observations on the offspring during neonatal growth.

Aspartame and its DKP were examined for reproduction and teratological effects in 24 such studies. One study was done in a chick embryo system (53); all others were done using rats or rabbits. In the chick embryo study (53), aspartame doses of 0.25 mg and 0.5 mg per egg, along with appropriate controls, were studied. No morphological abnormalities were reported in the embryos or hatched chicks of the aspartame treatment groups.

A segment I study of aspartame was performed using Charles River CD rats (54). Two dose groups composed of 14 male and 30 female rats each were given 2 and 4 g of aspartame per kilogram body weight per day, respectively, in the diet. The control group consisted of 14 male and 48 female rats fed a basal chow diet. All treated animals received aspartame in the diet during the premating and mating period; the females continued to receive aspartame during gestation and lactation. Some animals were sacrificed at the end of the mating period. Fifty percent of the dams were sacrificed at day 13 of gestation; the ovaries, uterus, and uterine contents were examined. The remaining dams were allowed to go through gestation, delivery, and lactation. The pups were examined for evidence of malformation at birth and allowed to go to weaning (21 days), at which time they were sacrificed. Aspartame was reported to have no effects on paternal survival rate, mating performance, fertility, or body weight gain, even though paternal food consumption was depressed. With the exception of a few random fluctuations, maternal survival, body weight gain, and food consumption were unremarkable. No evidence of an aspartame effect was reported after examination of the data obtained from the hysterotomy, litter examination, or neonatal examination.

A multigeneration reproduction study was also performed in Charles River CD rats (55). As in the above experiment (54), aspartame was given in the diet at 0, 2, and 4 g/kg body weight per day throughout the study to groups of 12 male and 24 female rats. Aspartame administration began 9 weeks prior to mating the P_1 animals. All F_1 litters were reduced to 10 pups within 24 hr of delivery; these remaining animals were used as the P_2 group, 20 males and 60 females per group. The P_2 groups were mated at 9 weeks of age. Of the F_2 litters, five litters per group were killed at birth and used in preparing a separate clinical pathology report (56). The remaining 15 F_2 litters per group were followed to weaning (21 days) and sacrificed. Mean food consumption, body weight, survival, physical appearance, and behavior were recorded. Evaluation of the data indicated no difference between treated and control groups, with the exception of reduced mean body weight of weanling rats in both the F_1 and F_2 high-dose litters. Evaluation of the data relating to fertility, gestation, live births, and litter size at weaning indicated comparable findings between treated and control groups.

A segment II teratology study was done in Charles River CD rats (57). Aspartame was given as a diet admix to 24 mated females in each of three dosage groups (0, 2, and 4 g/kg body weight per day) during gestation days 6-15. On gestation day 20, all dams were sacrificed, the ovaries and uterus were removed, and the uterine contents examined. Fetuses were examined externally and preserved intact for subsequent soft tissue and skeletal examination. Forty-seven litters comprised of 589 fetuses were examined; no evidence of soft tissue or skeletal anomalies was observed. In addition, no differences were reported between control and treated groups with respect to the mean number of resorption

sites, fetuses per pregnant female, viable fetuses, fetal sex distribution, fetal body weight and length, and crown-rump distance. There were no effects reported on maternal survival or body weight. It was concluded that oral administration of up to 4 g/kg body weight per day aspartame during the 6th to 15th gestational day was neither embryotoxic nor teratogenic.

Four segment III teratology studies were done using Charles River CD rats (58-61). These studies were of the same design and yielded comparable results; therefore they will be reviewed as a unit. Three groups of 24 pregnant female rats each were given 0, 2.5, and 4.4 g/kg body weight per day aspartame during gestation days 14-21 (parturition) and 0, 3.6, and 6.8 g/kg body weight per day aspartame on postpartum days 1-21 (weaning). There were 21 litters (246 pups) from the control females, 20 litters (236 pups) from the low-dose females, and 22 litters (289 pups) from the high-dose females. All pups were examined at birth. No differences were reported between control and treatment groups with respect to maternal food consumption, behavior, mobidity, and mortality. Mean maternal body weights were depressed for the high-dose groups during the lactation period. Live birth data, litter size, and data from the physical examination of the pups were not remarkable. However, weanling pup survival was reported to be depressed for those pups in the high-dose group. In addition, 3% of the high-dose pups were reported to have incompletely opened eyelids, and two pups from the same high-dose litter had "grossly observable lens opacities" (58).

One other segment II study was carried out in rats fed a 3:1 mixture of aspartame and its DKP (62). Four groups each of 30 mated females were given the aspartame:DKP mixture in the diet at levels of 0, 1, 2, and 3 g/kg body weight per day from gestational days 6 to 14. On gestation day 19, all dams were sacrificed and their uterine contents examined as described above in study E-5 (57). Eighty-two litters (1026 term fetuses) from treated females were examined for soft tissue and skeletal anomalies. None were observed. No differences were noted between control and treated groups with respect to maternal survival, body weight, food consumption, mean number of implantation sites, resorption sites, number of fetuses per pregnant female, live fetuses, dead fetuses, fetal sex distribution, fetal body weight, or crown-rump distance.

Aspartame was studied in a total of six segment II teratology studies using New Zealand white rabbits. In five of these studies aspartame alone was fed (63-67), while in the sixth a mixture of aspartame and its DKP was fed in a 3:1 ratio (68). The design of these studies was identical; therefore they will be reviewed as a unit. In all studies, the female rabbits were artificially inseminated using pooled sperm specimens. Aspartame was administered by gavage at 2 g/kg body weight per day during gestation days 6-18 (63,64). The aspartame:DKP mixture was given by gavage at 3 g/kg body weight per day during gestation days 6-18 (68). In studies E-54, E-55, and E-79 (65-67), aspartame was administered as a pelleted diet at mean dosages of 1.1 and 1.9 g/kg body weight

per day. All animals were sacrificed at term and fetuses were examined externally. Approximately one-half of the fetuses were processed for soft tissue examination and one-half processed for skeletal examination. In addition, observations were made on maternal survival rates, conception rates, body weights, hysterotomy findings, litter size and viability, fetal size, and sex distribution. These reports concluded that there were no differences between the control and treated groups and that there were no compound-related embryotoxic or teratogenic effects.

Aspartame's diketopiperazine derivative was independently studied in a series of reproduction and teratology studies. Three studies (segments I-III) were carried out in Charles River CD rats (58,69), and one segment II study was carried out in New Zealand white rabbits (70). In the segment I rat study (58), aspartame's DKP was administered in the diet (14 males and 28 females in each dosage group) at 0.45, 0.9, and 1.8 g/kg body weight per day. A group of 14 male and 60 females served as controls. The diet was given throughout premating, mating, gestation, and lactation. The DKP was reported to have no effect on parental survival, food consumption, mating performance, fertility, or parental body weight gain. At the high-dose level, dam body weights were depressed during the midgestation period. It was concluded that DKP fed continuously had no adverse effects on the sires, dams, or pups.

File study E-37 (58) also contains the report of a segment III study of DKP in Charles River CD rats. In this study, four groups of 20 pregnant rats were fed DKP in a diet admix at 0, 0.7, 1.3, and 2.5 g/kg body weight per day from gestation day 14 to postpartum day 21 (weaning). The report concluded that there were no adverse effects attributable to DKP administration in this study.

The segment II DKP study (69) in rats consisted of four groups of 24 mated females fed aspartame's DKP at 0, 1, 2, or 4 g/kg body weight per day, respectively, from the 6th through the 15th day of gestation. In addition to evaluation for possible soft tissue and skeletal anomalies, observations were made on maternal survival, conception rate, body weight, food consumption, number of resorption sites, mean number of fetuses per pregnant female, fetal sex distribution, fetal body weight, and crown-rump distance. A significant decrease in resorption sites was reported for the high-dose group. No treatment-related anatomical alterations were observed.

A segment II study of DKP was performed using New Zealand white rabbits (70). Four groups of 21 artificially inseminated rabbits received 0, 0.5, 1, or 2 g/kg body weight per day of DKP by gavage from gestation days 6 to 18. While no embryotoxic or teratogenic effects were discerned, there were insufficient data from the high-dose group to permit a complete evaluation.

Aspartame and its DKP were subjected to a series of mutagenicity tests, ranging from in vitro to in vivo assays. Both aspartame and its DKP were tested twice each in the Ames *Salmonella*/microsome assay, with no mutagenic activity being observed in any assay (71-74). Both compounds were studied separately in the dominant lethal assay using Charles River CD rats (75,76), in the host

mediated assay using Purina Caesarean rats (77,78), and in in vivo cytogenetic assays using Holtzman and Purina Caesarean rats (79-81). In none of these assays was there evidence of genetic activity by either aspartame or its DKP.

CONCLUSIONS

The preclinical studies enumerated above, as well as clinical studies discussed elsewhere in this volume, formed the basis for deliberation by the Bureau of Foods of the U.S. Food and Drug Administration (FDA) and, subsequently, by the Commissioner of the FDA who made the final decision to allow aspartame as a food additive (1). This data base was also evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JEC/FA) and was the basis on which that body established an allowable daily intake (ADI) of 0-40 mg/kg body weight per day for aspartame and an ADI of 0-7.5 mg/kg body weight per day for aspartame's DKP (2). The acceptable daily intake established the the JEC/FA is based on no-observed-effect levels in the preclinical studies enumerated above of 4 g/kg body weight per day for aspartame and of 750 mg/kg body weight per day for aspartame's DKP. A safety factor of 100 was applied to these to arrive at the respective ADIs (2). Commissioner Hayes of the Food and Drug Administration, based on clinical data and projected consumption data provided by the G. D. Searle Co., took the 99th percentile of human consumption to be 34 mg/kg body weight per day (1). This figure, arrived at by a line of reasoning different from that of the JEC/FA, is remarkably close to the ADI for aspartame established by the JEC/FA.

The data from preclinical studies, such as those enumerated above, cannot by themselves assure that a food additive is completely safe for all segments of the consuming population. When integrated with the clinical data discussed elsewhere in this volume and with projected consumption data, there is reasonable certainty that aspartame will cause no harm to the public who consume it. Only use, concommitant with regulatory surveillance, can lead to a final determination of whether aspartame is safe for use by all segments of the population.

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*In the "E-file" reports by G. D. Searle to the Food and Drug Administration, SC-18862 refers to aspartame (Searle Compound 18862) and SC-19192 refers to aspartame's diketopiperazine (DKP) derivative (Searle Compound SC-19192).

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