DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[Docket No. 75F-0355]

ASPARTAME

DECISION OF THE PUBLIC BOARD OF INQUIRY

F-0355

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I. BACKGROUND

The Commissioner of Food and Drugs has appointed a
Public Board of Inquiry to conduct a hearing involving the
long-standing controversy concerning the safety of aspartame
for human consumption. Aspartame essentially is a dipeptide
composed of the amino acids phenylalanine and aspartic acid.
It has an intensely sweet taste, 180-200 times stronger than
that of sucrose.

In the Federal Register of March 5, 1973 (38 Fed. Reg.
5921), the Food and Drug Administration (FDA) announced that
a petition (FAP 3A2885) had been filed by G. D. Searle & Co.,
Box 5110, Chicago, Illinois 60680, proposing the issuance of
a food additive regulation to provide for the safe use of
aspartame (L-aspartyl-L-phenylalanine methyl ester) in foods
as a nutritive substance with intense sweetness and with
flavor-enhancing properties. The petition was filed under
section 409 of the Federal Food, Drug, and Cosmetic Act, 21
U.S.C. 348.

In the Federal Register of July 26, 1974 (39 Fed. Reg.
27317), FDA, after evaluating data in the petition and other
relevant material, issued a regulation, now codified at 21
CFR 172.804, prescribing the conditions under which aspartame
could be safely used. The regulation approved the use of

aspartame in food as a sweetening agent or for an authorized technological purpose in foods for which standards of identity established under section 401 of the Act (21 U.S.C. 341) do not preclude such use. Aspartame was specifically approved for use as a sweetener in the following foods:

(a) Dry, free-flowing sugar substitutes for table use (not to include use in cooking) in package units not to exceed the sweetening equivalent of 2 teaspoonfuls of sugar.

(b) Sugar substitute tablets for sweetening hot beverages, including coffee and tea. L-leucine was approved for use as a lubricant in the manufacture of such tablets at a level not to exceed 3.5 percent of the weight of the tablet.

(c) Cold breakfast cereals.

(d) Chewing gum.

(e) Dry bases for:

(i) Beverages;

(ii) Instant coffee and tea;

(iii) Gelatins, puddings, and fillings; and

(iv) Dairy product analog toppings.

Aspartame was also approved for use as a flavor enhancer in chewing gum.

The regulation required the label of any food containing aspartame to bear, either on the principal display or on the information panel, the following statement: "PHENYLKETONURICS: CONTAINS PHENYLALANINE." The regulation also required that when aspartame was to be used in a sugar substitute for table use, its label was to bear instructions not to use aspartame in cooking or baking. Finally, if the food containing aspartame purported or was represented for special dietary uses, it was required to be labeled in compliance with special dietary foods regulations.

John W. Olney, M.D., and, jointly, James S. Turner and LABEL, Inc. objected to the regulation and requested a formal evidentiary hearing on certain issues they identified concerning the safety of aspartame. According to these objections, aspartame should not have been approved as a substitute for sucrose, for the reason that it would expose the human being--and especially the unborn child and the infant--to a considerable risk of brain damage leading to

either mental retardation or endocrine dysfunction, or both.
Added to this objection were questions concerning a possible
potential of aspartame to contribute to the incidence of
brain tumors.

The two objecting parties subsequently waived their
right to a formal evidentiary hearing and requested, instead,
that the agency establish a Public Board of Inquiry to
consider the issues raised by their objections to the food
additive regulation. After a preliminary audit of Searle's
studies raised certain questions about how the studies were
conducted, FDA, in the Federal Register of December 5, 1975
(40 Fed. Reg. 56907), imposed a stay of the regulation
authorizing the use of aspartame and announced that the
establishment of a Public Board of Inquiry would be postponed
until the questions raised by the audit were resolved.

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The data in question were subsequently reviewed by FDA
and by the Universities Associated for Research and Education
in Pathology (UAREP). Both UAREP and FDA concluded that the
data submitted by Searle were authentic.

In the Federal Register of June 1, 1979 (44 Fed. Reg.
31716), the Commissioner announced that a hearing before a
Public Board of Inquiry would be held on the issues raised by
the objections to the aspartame food additive regulation.

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The questions addressed to the Board by the Commissioner are
phrased in the form of three Issues. One of these (Issue
Number 1) refers to the question whether aspartame consump-
tion indeed, as claimed by the objecting parties, might
entail a risk of brain damage resulting in mental retarda-
tion, endocrine dysfunction, or both. A second Issue (Issue
Number 2) phrases the question whether aspartame consumption
indeed, as claimed by the objecting parties, might increase
the incidence of brain tumors. The Board was then asked to
decide, based upon its answers to these two questions,
whether aspartame should be allowed for use in foods or
whether the approval of aspartame should be withdrawn (Issue
Number 3).

In accordance with 21 CFR 13.10, nominees for members of
the Public Board of Inquiry were submitted to the Commis-
sioner, and on August 16, 1979, the undersigned were selected
as members of the Board.

A prehearing conference was held by telephone on
January 14, 1980, between the Board and the following
persons who requested to participate in the hearing: the
Bureau of Foods of the FDA; G. D. Searle & Co.; Dr. Olney;
Mr. Turner; Lloyd J. Filer, Jr., M.D.; and Richard J.
Wurtman, M.D. Thereafter, pursuant to a Federal Register
notice of January 15, 1980 (45 Fed. Reg. 2908) announcing

the time and place of the hearing, evidence concerning the three Issues was submitted to the Board and heard at a public session in Rockville, Maryland, on January 30 through February 1, 1980. The Board also consulted at the hearing with William Nyhan, M.D., and Milton Brightman, M.D. Post-hearing briefs were filed by the Bureau of Foods, G. D. Searle & Co., Dr. Olney, and Mr. Turner. This Initial Decision represents the Board's deliberations over the evidence that was presented.

II. PRELIMINARY MATTERS

A. Mr. Turner's Request for Another Hearing

On February 27, 1980, Mr. Turner asked the Board to reconsider its decision at the public hearing not to consider certain information concerning the quality of the data contained in the record. Mr. Turner objected to the Board's decision, arguing that it was tantamount to a decision not to examine the "scientific validity" of the studies FDA relied on to establish the safety of aspartame. Mr. Turner argued that the Board is required to make such an examination as part of its responsibility to determine the safety of aspartame. In his appeal, Mr. Turner requested the Board to reconvene a public session to consider evidence on such issues.

The Board does not agree with Mr. Turner's statement that it has refused to hear evidence relating to scientific validity. Mr. Turner uses the term "scientific validity" to describe questions about the authenticity, reliability, and accuracy of the data submitted by Searle and relied on by the FDA in determining the safety of aspartame. Those questions were considered and resolved by the FDA and UAREP before convening this Board. Because it would be impossible for the Board to undertake a retrospective quality inspection of all the studies presented to it, the Board was not charged with making such an examination. The Board did not exclude evidence relating to the quality or appropriateness of the experimental design of the studies or the scientific conclusions that can validly be drawn from the studies. The Board believes that questions involving the proper interpretation of the data are, in fact, questions relating to scientific validity. Thus, although the Board has decided that it should not repeat UAREP's authentication of the data, it has not decided to ignore questions concerning the scientific validity of the studies.

The Board believes that its authority and responsibilities in this public proceeding are clearly delineated in the statement of issues published in the Federal Register of June 1, 1979 (44 Fed. Reg. 31716). Questions involving the authenticity, reliability, and accuracy of the data have

already been resolved by FDA and UAREP and, therefore, are
not encompassed within the scope of this hearing. Also,
the regulation prescribing the procedures to be followed by
the Board provides that the Chairman may schedule a second
hearing only if he concludes that such a hearing is necessary
in order to "fully and fairly present information that cannot
otherwise adequately be considered and to properly resolve
the issues." 21 C.F.R. 13.30(e). The Board has concluded
that, since it has not been asked by the Commissioner to
consider the types of questions raised by Mr. Turner, it is
not necessary to hold another hearing to consider such
evidence.

B. The Glutamate Association's Request to be Designated as a Participant

The first issue in this hearing is whether the ingestion
of aspartame, either alone or together with glutamate, poses
a risk of contributing to mental retardation, brain damage,
or undesirable effects on neuroendocrine regulatory systems.
On July 12, 1979, the Glutamate Association wrote to FDA
reserving the right to participate in this proceeding if
glutamate per se or its safety were called into question.
The Association restated its position in a letter to the
Board dated January 22, 1980.

On February 27, 1980, the Glutamate Association requested permission from the Board to participate in the proceeding for the purpose of providing for the record certain scientific comments prepared by the International Glutamate Technical Committee. The Association stated that it wished to participate because it believed that at the hearing Dr. Olney had raised questions relating to the safety of glutamate alone.

The Board has decided to grant permission to the Glutamate Association to participate in this hearing for the limited purpose of providing for the record scientific comments prepared by the International Glutamate Technical Committee. These comments are based on materials already in the record and, therefore, should not prejudice the other participants.

III. ISSUE NUMBER 1

The question has been raised whether the ingestion of aspartame, either alone or together with glutamate, poses a risk of contributing to mental retardation, brain damage, or undesirable effects on neuroendocrine regulatory systems. From available evidence, what can be concluded in relation to this question? The objecting parties believe that the ingestion of aspartame, either alone or together with glutamate, does pose a risk of contributing to these effects. The Bureau of Foods believes that the

> ingestion of aspartame, either alone or
> together with glutamate, does not pose a
> risk of contributing to these effects.
> 44 Fed. Reg. 31717.

The Board decided that this question needs to be addressed under two separate headings, one referring to the neurotoxic potential of aspartame's phenylalanine moiety, the second to the neurotoxic potential of its other amino-acid moiety, aspartic acid. The reason for this is that aspartame's two component amino acids are each associated with a particular form of brain damage: phenylalanine with the diffuse neuropathology underlying phenylketonuric mental retardation, and aspartic acid with a different and more focal form of nerve cell damage affecting foremost the infundibular region of the hypothalamus and thereby inducing endocrine disorders. Since both of aspartame's component amino acids, phenylalanine and aspartic acid, are normal constituents of nearly all of the protein structures that compose our bodily tissues, are normally present in blood plasma, and are ingested in considerable amounts as components of natural foods, animal as well as vegetable, it is a priori clear that they can exert their respective neurotoxic effects only when reaching abnormally high concentrations in the blood plasma. Such hazardous concentration could be thought to result either from excessive oral ingestion or parenteral administration

(systemic injection) of these amino acids, or--as in the case

of phenylketonuria--from the absence of an enzyme crucially

involved in their metabolism.

The questions to be addressed with respect to both amino

acids composing the aspartame molecule follow naturally from

these considerations. They are:

1. At what concentration in the blood plasma do the
    amino acids at issue begin to pose a risk of brain
    damage?

2. In what amount would aspartame have to be consumed
    to induce such hazardous plasma--amino acid
    concentrations, either when ingested alone or when taken
    together with foods or with other food additives?

A. Diffuse Brain Damage Associated With
    Abnormally High Plasma-Phenylalanine
    Levels: Phenylketonuria

Phenylketonuria (PKU) is an inherited disorder in the

metabolism of phenylalanine. It is transmitted by an

autosomal recessive gene, and its incidence in the United

States is about 1 in 15,000. The disorder results from the

absence of an enzyme (phenylalanine hydroxylase) that

converts phenylalanine (PHE) to tyrosine; as a consequence

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PHE accumulates in body tissues--including blood--in
abnormally high concentration: in untreated phenylketonurics
plasma-PHE levels usually range between 120-600 μmol/dl
(20-100 mg %) instead of the normal 6-12 umol/dl. Through
mechanisms not yet fully understood, these grossly elevated
PHE concentrations are correlated with severely impaired
development of the immature brain in general, and of the
myelin sheaths of its nerve fibers in particular. The
clinical consequence of this developmental impairment is a
profound mental retardation, often accompanied by epileptic
seizures and chronic dermatitis. Children born with the
enzyme deficiency can develop to adults of normal
intelligence, provided their condition is recognized soon
after birth, and appropriate dietary treatment instituted
promptly thereafter. It is estimated that the PKU newborn
loses one percentage point of future intellectual capacity
for each postnatal week the condition goes unrecognized (cf.
Dr. Richard Koch's testimony at the public hearing).
Treatment is aimed at keeping plasma-PHE concentrations at or
below 70-80 umol/dl by restricting the dietary intake of PHE.
If this preventative regimen is to be successfully
maintained, families with a phenylketonuric child must impose
upon the child a strict dietary discipline that cannot be
relaxed until the child is adolescent. It is important to
note, however, that phenylketonuric mental retardation is
conditional upon sustained high plasma levels of PHE, in

contrast to the more focal brain damage that can result--as
will be emphasized in a subsequent section--from a single,
short-lived surge of glutamic or aspartic acid concentration
in the blood plasma.

The essential question with which the Board found itself
confronted in examining the phenylalanine issue is: at what
level of ingestion could aspartame induce a rise in
plasma-PHE concentration to 100 μmol/dl or higher--the levels
associated with impaired brain development? It is clear that
this question is of particular importance in the case of
children under 12, whose brain is still immature, and in the
case of women in the child-bearing age. The importance of
the question for the latter category is accentuated by the
well-established fact that the placenta maintains between the
maternal and fetal circulations a 1:2 gradient in the plasma
concentrations of most amino acids, including phenylalanine.
This means that for the fetal plasma-PHE concentration to
reach the 100 umol/dl level, the maternal plasma-PHE
concentration needs to rise no higher than 50 umol/dl.

Of the evidence presented the Board considers the
following data of particular significance:

1. In normal human adults, the ingestion of a single
loading dose of 34 mg/kg body weight aspartame (the 99th

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percentile of projected aspartame consumption for an entire day) dissolved in orange juice induces a rise in plasma-PHE concentration from a fasting level of 6 μmol/dl to 11 μmol/dl, a level normally found in adults and children following ingestion of a protein-rich meal. This peak value is reached about one hour after the aspartame ingestion, and recedes to fasting level within about 8 hours.

Ingestion of larger loading doses induces proportionately higher plasma-PHE elevations. A 50 mg/kg loading dose (in a 60 kg person 3000 mg aspartame, or 150 aspartame tablets, or 6 liters of aspartame-sweetened beverage, but with its 50% content of PHE equivalent to less than half the 4000 mg PHE contained in one 4-oz. hamburger) causes the plasma-PHE level to rise from 6 to 16 μmol/dl. Following a 100 mg/kg loading dose (equivalent to 12 liters of aspartame-sweetened beverage consumed in a single setting) the plasma-PHE level rises to 20 μmol/dl. Only a 200 mg/kg loading dose was found to induce a rise to 50 μmol/dl, and only following this very large dose did the plasma-PHE concentration take more than 8 hours to return to baseline. This 200 mg/kg dose corresponds to 600 aspartame tablets, or 24 liters of aspartame-sweetened beverage consumed in a single sitting by a 60-kg adult, or to 100 tablets of 20 mg aspartame accidentally ingested by a 3-year old child. Only in this grossly abusive amount could aspartame ingested by a

pregnant woman be expected to induce plasma-PHE concentrations high enough to cause, through placental transfer, fetal plasma-PHE levels approaching--for a few hours at least--the lower limit of potential toxicity. However, it seems inconceivable that so large a dose would be taken in a single sitting. When consumed over a 16-hour period--as would seem nearly unavoidable--it would undoubtedly induce a more sustained plasma-PHE elevation remaining well below the 50 umol/dl peak induced by the same amount of aspartame taken as a loading dose.

2.   In the normal one-year old infant, a loading dose of 34 mg/kg body weight causes the plasma-PHE concentration to rise from a fasting level of 6 umol/dl to 10 μmol/dl, receding to baseline within 4 hours. It appears from this finding that the 1-year old normal child metabolizes PHE at least as effectively as does the normal adult.

3.   In individuals heterozygous for phenylketonuria, a 34 mg/kg loading dose of aspartame induces a higher and longer-lasting plasma-PHE elevation. Instead of the 11 μmol/dl peak resulting from such a loading dose in the normal human, the peak reaches 16 μmol/dl in the PKU heterozygote and, in addition, the plasma-PHE curve declines more slowly than it does in normal individuals. A loading dose of 100 mg/kg aspartame--an abuse load even when ingested over a

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16-hour period--is followed by a plasma-PHE rise reaching 42 umol/dl, about twice as high as in the normal human. Even following this enormous single load, however, the peak value remains below the level at which, in the case of a pregnant woman, a risk to her unborn child might arise. Moreover, an abuse dose of 100 mg/kg aspartame would in the real-life situation not be ingested in a single sitting, as it was in the cited experiments, but, rather, consumed over an extended time period. Under these more natural conditions, the plasma-PHE concentration could be expected to remain well below the 42 umol/dl level. It is of interest to note that a 100 mg/kg intake of aspartame by a 60-kg woman would add less to her dietary PHE consumption than would be added by an extra 4-oz. hamburger: 3000 instead of 4000 mg PHE.

4. Undetected cases of phenylketonuria. The question has been raised whether a risk might occur in unidentified PKU children as a consequence of the presence of aspartame in the food supply. The number of children in this category is unknown but thought to be very small. Screening of newborns for PKU is mandatory in 47 states, and it has been estimated that about 10% of the 200 PKU children born annually in the United States might remain undiagnosed and hence at great risk to grow up retarded (cf. Dr. Richard Koch's testimony at the public hearing). An undetected phenylketonuric infant would be adversely affected by the phenylalanine provided in

breast milk protein (or infant formula) which may furnish
levels of phenylalanine intake in the vicinity of 80
mg/kg/day. (This compares with a projected mean
phenylalanine intake from aspartame in children under 2 years
of 3 mg/kg/day). The argument that aspartame in the food
supply would significantly increase the risk of mental
retardation in the unidentified phenylketonuric is not
supported by these considerations. An undiagnosed PKU child
is at risk first and foremost by being undiagnosed and hence
permitted to consume meals that are standard for normal
children. This point is emphasized further under the next
item of consideration.

5. PKU children who are not on a restricted diet. As
PKU children get older they may be allowed larger helpings of
"free" food or they even go off their earlier restricted
diet. This may not be harmful provided that the child's
toleranée to phenylalanine is carefully monitored by blood
tests. However, the question arises whether the availablity
of aspartame in the food supply would compromise the health
and well-being of PKU children in this category. There
appear to exist no explicit data based on controlled studies
to answer this question, but it is possible to seek an answer
by considering the amounts of phenylalanine that such
children would be exposed to through usual food sources, in
comparison with the PHE provided by aspartame. For example,

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a 4-oz. hamburger supplies about 4000 mg phenylalanine, and a
normal child would consume an average of about 200 mg phenyl-
alanine per kg/day from normal food protein sources. This
intake level compares with a projected daily aspartame-based
phenylalanine intake of 17 mg/kg by those children whose
aspartame consumption would reach the upper 99th percentile
of the population. (For a 30-kg child this would correspond
to a daily consumption of 2 helpings of aspartame-coated
breakfast cereal plus 8 cans of aspartame-sweetened bever-
age). Thus, for children on an unrestricted diet aspartame
ingestion even at this high level would contribute less than
10% of the total daily PHE intake. For children whose
protein intake is restricted the relationships between food
protein-derived and aspartame-derived phenylalanine would
differ, but again the total intake provided by aspartame
remains small. In considering the daily variation in protein
intake and the concentration of phenylalanine provided by
normal foods it is evident that the ingestion of aspartame
could not pose a significant extra risk to PKU children whose
diet is either not restricted or only partially restricted.
The significant risk to their health is clearly from the
phenylalanine in the protein furnished by standard foods: in
a 30 kg youngster one extra hamburger would add 100-150
mg/kg, one extra hot dog about 50 mg/kg, one extra glass of
milk 15 mg/kg or nearly as much as the total amount of PHE

supplied by a 34 mg/kg intake of aspartame.

6. Hyperphenylalaninemia. This term refers to a
condition in which plasma-PHE levels anomalously range
between 25 and 120 μmol/dl. Most of those afflicted with
this abnormality are of normal intellect, and since they are
usually asymptomatic also, neither they nor others are likely
to be aware of their condition unless it had been identified
by a newborn-screening test. The incidence of hyperphenyl-
alaninemia is about 1/30,000, and it has been estimated that
in the United States the condition affects about 1750 women
of childbearing age. It is this latter category that gives
the most reason for concern, since the 50% among these women
who have plasma-PHE levels ranging between 60 and 120 umol/dl
are at high risk of giving birth to brain-damaged children
destined to grow up mentally retarded. The only effective
prevention of this consequence of hyperphenylalaninemia would
consist in a systematic reduction of dietary PHE intake
throughout pregnancy--in other words, in treating the
prospective mother much as a phenylketonuric child would be
treated. Such prophylactic measures, however, are naturally
contingent upon identification of the anomalous condition
before or shortly after the beginning of the pregnancy. It
follows that until such time as all hyperphenylalaninemics
are identified by screening tests a complete prevention of

congenital brain damage caused by maternal hyperphenyl-
alaninemia cannot realistically be hoped for.

In evaluating the risk inherent in aspartame consumption
by hyperphenylalaninemics, it is obvious that aspartame as a
source of PHE can only contribute further to the already high
plasma-PHE levels. It should be considered, however, that
even the unlikely abuse intake of 100 mg/kg of aspartame per
day by a 60-kg woman would supply less PHE (3000 mg) than
would be supplied by an extra 4-oz. hamburger (4000 mg), and
that the more likely (although still very high) intake of 34
mg/kg/day would be the PHE-equivalent of little more than two
extra glasses of milk. It thus seems fair to conclude that
the hyperphenylalaninemic woman is at much higher risk from
the consumption of natural foods than she would be from the
use of aspartame. It should be reiterated that the real
problem of hyperphenylalaninemia lies in the usually covert
nature of the anomaly.

Conclusions Regarding Aspartame-Induced Mental Retardation

In the Board's opinion, aspartame consumption by normal
humans cannot be expected to increase the incidence of that
particular form of mental retardation that is associated with
sustained elevation of plasma-PHE levels to (or beyond) 120
μmol/dl during immature stages of brain development. This

conclusion is based on the consideration that even the highly unlikely daily consumption level of 100 mg/kg of aspartame (3 times the projected upper one-percentile of aspartame consumption) would add no more than 15-20% to the normal dietary PHE intake, less than would be added in a 60-kg individual by an extra 4-oz. hamburger. Consumed at the estimated upper one-percentile level of 34 mg/kg/day, aspartame would increase the normal daily intake of PHE by no more than six percent. These figures lie well within the limits of day-to-day variations in dietary protein consumption.

In individuals on a PHE-restricted diet designed to prevent critically elevated plasma-PHE levels, aspartame is to be handled as any other source of phenylalanine. Since these individuals (phenylketonuric children and pregnant women known to have hyperphenylalaninemia) would follow a carefully prescribed diet, a cautionary label explicitly identifying aspartame as a PHE source should forestall a liberal use of this sweetener by such patients.

In the unfortunate case of unidentified hyperphenylalaninemia, the normal food-derived PHE poses a much greater risk to the patient (or the unborn child) than would aspartame, even when consumed in very large amounts. The hyperphenylalaninemic gravida not on a PHE-restricted

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diet would add 5-6% to her dietary PHE intake when consuming aspartame at the projected upper one-percentile level.

B. Focal Brain Lesions

Since first demonstrated in 1969 by Olney and co-workers in the mouse, it has become generally recognized that the acidic, dicarboxylic amino acids glutamic acid (GLU) and aspartic acid (ASP), when present in the blood plasma in adequately high concentration, can cause death of nerve cells in the central nervous system. As far as is known at present, this neuronal necrosis is focal rather than diffuse; it is certain that it preferentially affects (1) the infundibular region of the hypothalamus, (2) the so-called circumventricular organs (the area postrema, the subfornical organ, the subcommissural organ, the vascular organ of the lamina terminalis), and (3) the retina.

The evidence that acidic amino acids are potential neurotoxins naturally has raised questions with respect to the safety of aspartame as a food additive. Roughly one half of aspartame's molecular weight is contributed by its aspartic-acid moiety, and it is appropriate to ask whether its consumption could entail a risk of focal brain damage. Before considering the evidence it is necessary to point out that there are at least two reasons why this question

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concerning aspartic acid cannot be examined separately and must be considered together with a similar question concerning glutamic acid, a food additive already in wide use in the United States and elsewhere: (1) both of these amino acids appear to be equipotential and mutually additive in their neurotoxic effects, and (2) a significant proportion of ingested aspartic acid in the course of its metabolism is transaminated to glutamic acid. For these reasons, it is the combined GLU-ASP content of blood plasma that ultimately must be considered, rather than the plasma ASP level alone. It is also for these reasons that the Board permitted a voluminous body of data concerning glutamic acid to be presented, even though aspartame itself is free from this amino acid. Throughout the following survey of data it is assumed that glutamic acid or monosodium glutamate (MSG) is exchangeable with aspartic acid or sodium aspartate in the sense that the neurotoxic threshold levels of these substances in the blood plasma appear to be approximately the same.

Focal Brain Lesions Induced in Experimental Animals by Monosodium Glutamate

There is general agreement among investigators that high doses of MSG administered either by subcutaneous, intraperitoneal or intravenous injection, or by gavage

(stomach intubation), can induce hypothalamic lesions in a variety of rodent species. Of all experimental animals used in such experiments the infant mouse, 1-10 days old, has been found most vulnerable to the neurotoxic action of MSG: a single dose of 350 mg/kg injected subcutaneously, or of 500 mg/kg administered by gavage, is enough to cause, within a few hours time, a microscopically visible lesion of the hypothalamus in about half of the infant mice so treated. Correlated with this 50%-effectiveness level of intake is a rise in plasma-GLU concentration from a baseline value of about 15 μmol/dl to 100 μmol/dl. With increasing maturity mice become more resistant to MSG: in weanling mice a 50% effect requires an MSG dose of 1200 mg/kg administered by gavage and resulting in a plasma-GLU concentration of about 380 μmol/dl. In adult mice the critical plasma-GLU concentration lies near 600 μmol/dl.

Other non-primate mammalian species seem generally less vulnerable to the neurotoxic action of MSG. Although the infant rat is nearly as sensitive to MSG as the infant mouse, the 50%-effect dose in the adult rat lies near 4000 mg/kg by gavage. The critical dose in the 2-3-day old guinea pig is about 2000 mg/kg. In dogs 3-35 days old an intake of 1100 mg/kg by gavage fails to induce hypothalamic lesions, as do doses of up to 4000 mg/kg in adult dogs.

Data for the monkey are controversial. The Board is unable to resolve the conflicts that arose over this issue at the public hearing. However, to remain on the side of safety it accepts the claims: (a) that a dose of 1000 mg/kg of MSG administered by gavage or subcutaneous injection can cause microscopically detectable hypothalamic lesions in infant monkeys ranging between prematurely born and 7 days of age, and, (b) that intravenous injection of 2000 mg/kg of MSG in the pregnant monkey can induce such lesions in her fetus. Despite existing controversies the Board also accepts the suggestion that the plasma-GLU level critical for the occurrence of hypothalamic lesions in the immature monkey lies in the vicinity of 120 umol/dl.

MSG neurotoxicity in pregnant or lactating animals appears to have been studied only in a small number of species. Two separate groups of investigators have reported that in the pregnant mouse MSG must be injected in very large amounts (5000 mg/kg) to induce hypothalamic lesions in her fetuses. This finding accords well with the evidence (considered in more detail below) that the placenta in the monkey maintains a highly effective barrier against both GLU and ASP: only at grossly elevated maternal plasma-GLU levels (280 umol/dl) does GLU in this mammalian species begin to enter the fetal circulation. A somewhat similar barrier appears to be maintained by the mammary gland: in the

lactating human female at least, the ingestion of relatively
high doses of MSG does not significantly affect the GLU
content of her milk (see below).

Dietary intake of MSG by experimental animals. In all
of the animal experiments mentioned in the foregoing account,
MSG was either injected, or administered by stomach tube in
the form of an aqueous solution. Markedly different effects
upon plasma-GLU concentrations have been reported from
experiments in which mice were given MSG mixed with food.
Mixed with "infant formula" or with a "soup diet," and
administered by stomach tube, MSG in weanling mice has been
reported to induce a rise of the plasma-GLU concentration
only one-fifth to one-third as large as that caused by the
same amount of MSG mixed with water. Ingested by adult mice
as a food additive in the enormous amount of 20,000 mg/kg,
MSG has been reported to induce peak plasma-GLU
concentrations no higher than 174 μmol/dl, little more than
one-quarter of the plasma level (630 umol/dl) that is
correlated with hypothalamic lesions caused by subcutaneous
injection of 1500 mg/kg MSG. It is relevant in this context
that the archival literature includes no report of brain
lesions induced in any species by dietary intake of any
amount of MSG.

A postscript to these negative findings must be made.
In a post-hearing communication dated April 3, 1980, to the
Board and to his co-participants in the hearing, Dr. Olney
reported having found clear-cut hypothalamic lesions in all
of 10 weanling mice who--after having been deprived of water
overnight--had drunk 0.2-0.35 ml of either a 10% aqueous GLU
(presumably l-glutamic acid) solution or a solution
containing 6.5% GLU, 3.5% ASP, and 1% aspartame, while
concurrently consuming an unspecified amount of Purina mouse
chow. The Board accepts this evidence (acknowledging that it
stands at present unconfirmed) and considers that it imposes
a qualification upon those statements according to which no
focal brain lesions have been induced in any species by
voluntary consumption of any amount of GLU or its monosodium
salt. A rough calculation suggests that the weanling rats
had ingested a minimum of 13 mg of GLU with the drinking
water. Assuming that body weights ranged between 10 and
15 g, this intake corresponds to a loading dose of 900 mg/kg
to 1300 mg/kg body weight.

Focal Brain Lesions Induced in Experimental Animals by Aspartame

In the infant mouse, 2000 mg/kg aspartame administered
by gavage in the form of an aqueous slurry has been reported

to cause hypothalamic lesions in 39% of subjects. No such
lesions were found in any 9-day old mouse given 500 mg/kg
aspartame by gavage. It seems reasonable to assume that in
the infant mouse the risk of hypothalamic lesion begins to
arise at a dose level of 1000 mg/kg aspartame administered by
gavage. This dose approximately corresponds to 500 mg/kg
aspartic acid.

Since neither the same dose nor very much higher doses
of aspartame consumed by immature mice as part of the daily
diet have been found to induce endocrine disorders (see
below) it seems warranted to conclude that the resorption
and/or metabolism of aspartic acid depends upon the route by
which this amino acid is administered. Much like MSG,
aspartic acid ingested as a food additive has been reported
to induce elevations of the plasma-ASP level smaller than
those induced by aspartic acid administered by gavage or
subcutaneous injection. Further data concerning this point
will be considered in a subsequent review of aspartame
consumption in the human.

Neuroendocrine Disorders Induced by MSG and Aspartame in Experimental Animals

In view of the topographic characteristics of its neurotoxic effects it is not surprising that MSG administered in large amounts by subcutaneous injection has been found to induce endocrine disorders in mice, rats, and hamsters. In all of the studies from which such disorders were reported, subjects had received either a single subcutaneous injection of 3000 mg/kg MSG on the second postnatal day, or a daily injection of 2200-4000 mg/kg for 10 days starting on day 2. Prominently listed among the consequences of such treatments are: stunting of body growth, obesity, and sterility in the female. Although apparently not explicitly demonstrated thus far, it seems reasonable to assume that in the same species subcutaneous injection of similar amounts of aspartate, or administration of aspartame by gavage in twice these amounts, would have similar endocrine consequences. It must be stressed, however, that no studies concerning the endocrine effects of subcutaneous or intragastric administration of either MSG or aspartate appear to have been done in species other than rodents. Hence, at present nothing can be said concerning the relative susceptibility of the endocrine system of various non-rodent species to parenterally administered MSG or aspartate.

Neuroendocrine Effects of Sub-neurotoxic Doses of MSG and Aspartame

One of the objecting parties has stressed the possibility that a routine intake of MSG or aspartame several times a day by children throughout their formative years could entail repetitive disturbances in several neuroendocrine axes (e.g., gonadotropins, growth hormone, and prolactin) and that such perturbations could adversely affect somatosexual development. According to this suggestion, neuroendocrine disorders induced by MSG or aspartame need not be associated with anatomically demonstrable lesions of the hypothalamus, and can be caused by an imbalance of hypothalamic function resulting from the neuroexcitatory effect of glutamate and aspartate. The notion is based upon a report by the objecting party according to which a subcutaneous injection of MSG in the presumably sub-neurotoxic amount of 1000 mg/kg in the adult rat markedly elevates plasma levels of luteinizing hormone (LH) and testosterone (TS). It was pointed out at the hearing, however, that quantitatively similar fluctuations of LH and TS levels occur normally in the course of each 24-hour period, and that the reported increases may thus have reflected no more than a normal circadian or ultradian periodicity of LH and TS release. Moreover, in two other

published studies no correlation between MSG injections and
fluctuations of LH and TS levels could be demonstrated.

The suggestion that a routine intake of aspartame during
immature stages of development can entail an impairment of
sexual function in later life would seem effectively refuted
by the results of a long-term study of the effects of
aspartame consumption on reproductive function in the rat.
In this study, a daily dietary intake of very large amounts
of aspartame ranging between 1800 and 3700 mg/kg, beginning
on postnatal days 10-20 and ending on days 90-100, did not
affect fertility, gestation, live birth, litter size, or
nursing in either the experimental subjects or their
offspring. The results of several further studies presented
at the hearing likewise indicate that endocrine disorders are
induced by MSG only when this substance is administered in
amounts large enough to cause identifiable hypothalamic
lesions. The experimental evidence thus appears to argue
against the notion of sub-neurotoxic effects upon the
neuroendocrine axis.

Glutamate and Aspartame Consumption in the Human

Among the data presented on this subject, the Board
considers the following pragmatic evidence of particular
relevance.

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1. In the adult, a loading dose of 34 mg/kg aspartame (the 99th percentile of a projected mean daily consumption of 7-9 mg/kg, and roughly equivalent to 100 tablets of 20 mg aspartame) dissolved in orange juice induces no significant elevation of either plasma GLU or plasma ASP concentration. Neither does a loading dose of 50 mg/kg aspartame induce any significant rise of GLU or ASP concentration in either blood plasma or erythrocytes.

2. A similarly administered aspartame loading dose of 200 mg/kg in the adult (equivalent to 600-800 aspartame tablets) causes the plasma ASP level to rise from a baseline of 0.2 μmol/dl to 1 umol/dl, receding to baseline in 3 hours. Following such a dose, the plasma GLU level rises from 2.5 μmol/dl to 6 umol/dl for a combined plasma GLU + ASP rise to 7 μmol/dl.

3. A hamburger-milkshake meal providing 1 g of protein per kg body weight, and containing free plus protein-bound GLU in the amount of 171-198 mg/kg body weight and free plus protein-bound ASP in the amount of 90-103 mg/kg body weight, causes an elevation of the plasma GLU level from a baseline of 4 μmol/dl to 9 μmol/dl, and raises the plasma ASP level from a baseline of 0.3 μmol/dl to 0.8 μmol/dl. The addition of 34 mg/kg MSG (the 90th percentile of projected MSG consumption) to this meal has no effect upon these

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post-prandial elevations, and neither does the addition to the meal of 34 mg/kg MSG plus 34 mg/kg aspartame. If the MSG addition to the meal is increased to 150 mg/kg the plasma GLU + ASP level rises from a baseline of 5 umol/dl to 25 umol/dl; the addition of 34 mg/kg aspartame in this case causes no further increase in the plasma GLU + ASP level.

4. **In one-year old infants**, a loading dose of 100 mg/kg aspartame induces a rise of the plasma ASP level from a baseline of 1.5 μmol/dl to 2.6 umol/dl, receding to baseline in 1-2 hours. This finding appears to refute any suggestion that aspartic acid might be metabolized less efficiently in infants than in adults.

5. **In PKU heterozygote** adults aspartame loading doses of 34 mg/kg and 100 mg/kg are metabolized much as they are in normal individuals. The resulting rise in plasma GLU level is virtually the same in both categories of subjects, while the rise in plasma ASP level is slightly, but not significantly, higher: plasma GLU + ASP level reaches a mean of 4.5 μmol/dl in normal adults, a mean of 4.8 μmol/dl in PKU heterozygote adults.

6. **In the lactating woman**, a loading dose of 50 mg/kg aspartame (about 150 aspartame tablets) induces no significant elevation of plasma ASP or GLU levels. This

dosage raises the ASP concentration in her milk from 2.3 to 4.8 umol/dl, the GLU concentration from 109 to 120 umol/dl. At this high level of maternal aspartame intake, the breast-fed infant's normal daily intake of 366 mg/kg GLU + ASP is increased by no more than 0.77 mg/kg.

7. Placental transfer of ASP to the fetus. For obvious reasons, this problem cannot be directly approached experimentally in the human. The following conclusions are based upon experiments in pregnant monkeys.

The primate placenta maintains a 1:2 plasma-concentration gradient toward the fetal circulation for most amino acids. However, both GLU and ASP are exceptions to this rule. GLU is not transferred at all from the maternal to the fetal circulation even when the maternal plasma level is increased from a baseline of 5 umol/dl to 55 µmol/dl; only at the enormously elevated maternal plasma GLU level of 280 umol/dl--induced by direct intravenous infusion of GLU--does some transfer to the fetus take place. The placenta maintains an equally effective barrier against ASP: intravenous infusion of 100 mg/kg ASP (in one hour) elevates the maternal ASP level from a baseline of 0.4 umol/dl to 80 umol/dl; the fetal plasma ASP level under these conditions does not exceed 0.42 umol/dl. Maternal ASP infusion of 200 mg/kg/hr induces a maternal plasma ASP rise to 237 umol/dl,

while the fetal plasma ASP level rises from a baseline of 0.6 umol/dl no further than 4.5 umol/dl.

Taken together with items 1 and 2 above, these findings indicate that both mother and fetus are thoroughly protected against hazardous plasma ASP levels: the mother by a highly effective barrier of ASP resorption and/or metabolism, the fetus in addition by an equally effective placental barrier. The mother herself has no comparably effective defense against GLU, but plasma GLU levels high enough to place her at risk are not reflected in the fetal blood plasma.

Risk Evaluation

In attempting to assess the risk of focal (in particular, hypothalamic) brain damage connected with human aspartame consumption, the Board decided to adopt a 100 umol/dl concentration of GLU + ASP in the blood plasma as the critical level. This conservative assumption was made for reasons of caution: 100 μmol/dl is the concentration at which a 50% occurrence of focal brain lesions has been reported for the infant mouse, the animal form generally thought to be most sensitive to the neurotoxic effects of glutamic and aspartic acid. The problem thus became reduced to the question whether, and at what level of consumption by the human, aspartame could induce plasma GLU + ASP elevations

approaching the 100 μmol/dl level when taken alone, or
alternatively, whether it could significantly contribute to
such elevations induced by MSG consumption. It should be
recalled in this connection that--unlike the brain damage
associated with phenylalanine--the focal brain lesions
associated with GLU and ASP neurotoxicity are not contingent
upon a long-maintained high plasma concentration of the
causative agent: it is evident from animal experiments that
focal hypothalamic lesions can be induced by a single
elevation of the plasma GLU and/or ASP concentration to the
level of 100 umol/dl.

It is of some historic interest that much of the
evidence reported to the Board concerning the aforementioned
question dates from recent years (1976-1979), and conse-
quently was not available at the time the objections to the
approval of aspartame as a food additive were originally
filed. With a single exception, the following statements can
at present be considered justified by the results of experi-
ments done directly in the human rather than in one or more
animal species:

1. The human organism, infant as well as adult, is
protected against high surges of ASP concentration in either
blood plasma or erythrocytes by a biological barrier
mechanism presumably located in the gastrointestinal mucosa

and/or liver. The effectiveness of this protective mechanism
is illustrated by the observation that loading doses of
aspartame as high as 200 mg/kg body weight (in a 60 kg
individual equivalent to 600 aspartame tablets or 20 liters
of aspartame-sweetened beverage consumed in a single sitting)
induces an elevation of plasma and erythrocyte GLU + ASP
concentration of no more than 5 umol/dl above a baseline
level of 2.5-3 umol/dl. It is of added significance that
these elevations are short-lived, receding to baseline in
about 3 hours time. It follows that repeat-doses of the same
enormous magnitude, when spaced 3 hours apart, are unlikely
to escalate the GLU + ASP concentration much beyond the level
induced by the first dose.

    2. The ASP plasma-entry barrier is unaffected by
simultaneously ingested MSG: the 25 umol/dl plasma GLU + ASP
concentration achieved by adding to a protein-rich meal a
very large dose of MSG (150 mg/kg, or 9000 mg in the case of
a 60 kg person) is not augmented by the further addition of
34 mg/kg aspartame (100 aspartame tablets) to the meal.

    3. The PKU heterozygote adult is no less effectively
protected against aspartame-induced surges of plasma GLU +
ASP concentration than the normal human.

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4. In the breast-fed infant, a consumption of 50 mg/kg aspartame by the lactating mother results in an increase of no more than 0.77 mg/kg GLU + ASP over the normal daily intake of 366 mg/kg GLU + ASP.

5. The speculation that aspartame consumption by the pregnant woman could expose her fetus to a high risk of focal brain damage cannot be investigated directly in the human. However, experimental findings in the monkey indicate that the primate placenta maintains a nearly insurmountable barrier against any transfer of GLU and ASP from the maternal to the fetal circulation.

Conclusion Regarding Aspartame-Induced Focal Brain Lesions

In the Board's opinion, the most pertinent evidence presented at the public hearing convincingly demonstrates that _the risk of focal brain damage associated with aspartame consumption in the human is negligible_. Elevations of plasma GLU + ASP concentration even to the lowest level that could be suspected of being neurotoxic (100 µmol/dl) would require an inconceivably high oral aspartame intake. Such levels might in fact prove attainable only by parenteral ASP administration designed to bypass the highly effective intestinal and/or hepatic barrier mechanism guarding against surges of plasma ASP concentration.

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C. Conclusion Concerning Issue Number 1

On the basis of the data reported at the public hearing, the Board concludes that the ingestion of aspartame, either alone or together with glutamate, cannot be expected to increase the incidence of mental retardation, brain damage, or dysfunction of neuroendocrine regulatory systems.

IV. ISSUE NUMBER 2

> The question has been raised whether the ingestion of aspartame may induce brain neoplasms in the rat. From available evidence, what can be concluded in relation to this question? The objecting parties believe that available evidence suggests, without adequately ruling out, a possible association between aspartame ingestion and an increased incidence of brain neoplasms in the rat. The Bureau of Foods believes that available evidence does not show that ingestion of aspartame results in an increased incidence of brain neoplasms in the rat. 44 Fed. Reg. 31717.

With respect to this question, it must be emphasized that the Board was compelled to base its judgment on no more than three studies in which the problem of aspartame's possible oncogenicity was systematically investigated. All three were reported by the defending party. In one of these studies (E33/34), four groups each of 80 rats of the Charles River/Sprague-Dawley strain were given doses of,

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respectively, 1000, 2000, 4000, and 6000-8000 mg aspartame
per kg body weight per day, starting after weaning and
continuing over two years; a group of 119 rats served as
untreated controls. In a second study (E70), two groups of,
respectively, 78 and 79 rats were given a daily dose of,
respectively, 2000 and 4000 mg/kg aspartame for two years;
these rats were the offspring of two groups of parents who
had been fed the same daily doses of aspartame, starting 60
days prior to mating and continued (in the mothers)
throughout gestation and lactation; 115 rats served as
untreated controls in this experiment. Finally, in a third
study (E77/78), the diketopiperazide (DKP) of aspartame was
examined for possible oncogenic effects by feeding this
compound to three groups of, respectively, 68, 66, and 64
rats in daily doses of, respectively, 750, 1500, and 3000
mg/kg, starting at 4 weeks and continued for 115 weeks; 123
rats were included in this study as untreated controls. From
the submitted reports, and from a personal viewing of the
histopathological material, the Board extracts the following
accounting:

1. In experiment E33/34 a total of 13 brain tumors were
found, 8 of which were large enough to have been noted upon
gross examination, and 6 of which may have contributed to
death before the end of the second year of life. In the
control group of 119 rats one brain tumor was found; it

consisted of a small, circumscript nodule, most likely a
metastatic carcinoma. In the second group (1000 mg/kg
aspartame/day), 4 gliomas were found; two of these were small
astrocytomas, the remaining two large, grossly visible, more
anaplastic gliomas (one of the latter caused--or contributed
to--death at 8 weeks). In the third group (2000 mg/kg/day) a
large glioma may have contributed to death at 16 weeks. In
the fourth group (4000 mg/kg/day) 5 gliomas were found, two
of which must have been noted at autopsy and may have been
the principal cause of death at 84 and 100 weeks,
respectively. In the fifth group (6000-8000 mg/kg/day) two
brain tumors, a glioblastoma and a medulloblastoma, caused
death at 66 and 12 weeks, respectively.

This study indicates a brain-tumor incidence of 0.8% in
the control group (1/119) and 3.75% in the aspartame-fed
rats. In view of the small number of 80 rats in each
experimental group, the two relatively low-dose (1000-2000
mg/kg/day) groups could be combined, as well as the two
high-dose groups. This would yield a figure of,
respectively, 5 brain tumors in 160 rats (3.1%), and 7 in 160
rats (4.3%), suggesting a possible dose-effect relationship.
Furthermore, it is noted that 8 of the 12 tumors in
aspartame-fed rats developed at less than 2 years of age.
The argument that the medulloblastoma should not be included
in the calculations cannot be accepted. In the human,

medulloblastomas are known to occur not only in infancy but also in older children, in adolescents, and occasionally even late in life. Moreover, in the oncological literature two medulloblastomas have been reported in adult Sprague-Dawley rats subjected to whole-body radiation.

2. In the E70 study 8 tumors were found in a total of 272 rats, corresponding to a combined incidence of 2.9%. Three of these 8 tumors were large enough to be identified grossly at the time of autopsy.

The most remarkable aspect of this study is the high incidence of brain tumors in the control group: 4 gliomas in 115 rats, or 3.5%. The remaining four tumors were found in the 157 rats exposed to aspartame from conception to 2 years of age: 2 gliomas in the low-dose group (2000 mg/kg), one glioma and meningioma in the high-dose group (4000 mg/kg), for a combined incidence of 2.5% brain tumors, or 1.9% gliomas, in the two experimental groups.

The overall incidence of 2.6% gliomas in this study (control plus aspartame-fed animals) is the highest thus far reported from lifetime studies on this strain of rats. Its most puzzling aspect is the 3.5% incidence of gliomas among the 115 control animals, a very high figure in comparison with the 0.8% incidence among the 119 control animals of the E33/34 study.

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3. In the E77/78 study concerning the diketopiperazide
of aspartame 5 tumors were recorded: 2 in the control group
of 123 rats (1.6%), the remaining 3 among the 198 animals of
the three experimental groups (1.5%). Two of the 5 gliomas
could have been noted on gross inspection of the brain.

This study shows no difference between experimental and
control groups, and the recorded percentages fall within the
high range of normal incidence reported from various
normative studies.

"Spontaneous" Occurrence of Brain Tumors Among Sprague-Dawley Rats

It is difficult to conclude from the archival literature
which of various published figures most accurately reflects
the "normal" (i.e., presumably non-toxogenic) incidence of
brain tumors in the Sprague-Dawley rat strain. Several
published reports are based on findings in rats that had been
used in long-term studies designed to check the potential
toxicity of a particular chemical compound, or of irradiated
foods. Other reports fail to state the protocol followed in
examining the brain for tumors: gross-anatomical tumor
identification only, or routine histological examination of
each brain? From the heterogeneous volume of published data,
the Board selected the following as most significant; first

of all because they seem most nearly normative (no potential
toxins were added to the diet), and, second, because the
brains were routinely examined histologically.

1. Thompson et al. (J. Nat'l Cancer Institute, vol. 27,
1961) recorded 4 brain tumors (3.2%) during the life span
(7-32 months) of 125 Sprague-Dawley rats. All occurred at
less than 2 years of age. One of the tumors was a glioma
(ependymoma), one a choroid plexus papilloma, one a
meningioma, and one a pinealoma (germinoma). The incidence
of gliomas in this study was 0.8% or 1.6% depending on
whether the papilloma is considered a glioma. The number of
rats used in this study is too small for a reliable
determination of spontaneous-tumor incidence.

2. Mawdesley-Thomas and Newman (J. Pathol., vol. 112,
1974) found 38 tumors of the central nervous system in 41,000
Sprague-Dawley rats (0.09%), seven of which were noted at
autopsy. Half of the tumors occurred after two years of age;
at 112 weeks only 20 tumors (0.046%) had been encountered.
Of the 38 tumors, 22 were gliomas, 13 meningiomas, and 3
sarcomas.

3. Fitzgerald et al. (J. Nat'l Cancer Institute, vol.
52, 1974) recorded 5 brain tumors in 650 rats: 4
astrocytomas and one meningioma (0.7%).

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To these three papers could be added one further
publication, by McKenzie and Garner (J. Nat'l Cancer
Institute, vol. 50, 1973), in which 535 rats were examined
that had been used in a 2-year study on the effects of
irradiated-food consumption. In this population, 3 brain
tumors, all gliomas, were found (0.6%).

According to these data, the "spontaneous" CNS-tumor
incidence in Sprague-Dawley rats varies between 0.09%
(Mawdesley-Thomas and Newman) and 3.2% (Thompson et al.). In
this context a remark by McKenzie and Garner is of interest,
according to which the tumor incidence in different groups of
"Sprague-Dawley" rats supplied by different commercial
sources differs from group to group as much as it differs
between the Sprague-Dawley and other rat strains. It is
therefore of possible significance that the Charles River CD
line of Sprague-Dawley rats used in the studies E33/34, E70
and E77/78 was also used by Fitzgerald et al. who arrived at
a 0.7% incidence of brain tumors and by McKenzie and Garner
who reported a 0.6% incidence.

Evaluation

The problem of aspartame's possible oncogenicity clearly
is a complex issue, difficult to judge fairly on the basis of
available data. Even with this reservation in mind, the

Board finds reason to be concerned about the evidence
submitted at the public hearing. Its concern rests mainly on
the outcome of study E33/34, as set forth in the following
account.

In study E33/34, a total of 320 rats received large
quantities of aspartame as a food additive. Twelve tumors
were found in these rats, 11 of which--or almost 90%--were
gliomas. By itself, the 3.5% incidence of brain tumors gives
cause for concern, and this is only augmented by the high
incidence of gliomas at relatively early age: 5 rats died
with glioma before completing the second year of life. In
the low-dose group (1000 mg/kg aspartame) one died at 8 weeks
of a large glioma; in the 2000 mg/kg group one died of glioma
at 16 weeks; the 3000 mg/kg group had one death of glioma at
84 weeks and one at 100 weeks, while there was one death of
glioblastoma at 66 weeks in the 6000-8000 mg/kg group. Thus,
study E33/34 yielded two deaths of glia-cell tumor in the
first year of life, and one at 66 weeks. By contrast, in
Mawdesley-Thomas and Newman's normative study involving
41,000 Sprague-Dawley rats no brain tumors were found in rats
younger than 60-70 weeks.

A further cause for concern in study E33/34 is presented
by the suggested dose-effect relationship: whereas the

combined brain tumor incidence in the two lower-dose groups
was 3.1%, it was 4.3% for the two higher-dose groups.

The outcome of the E70 study is puzzling. In the
Board's opinion, this critically important study should have
included a larger number of experimental animals. As it
stands, it is difficult or even impossible to evaluate with
respect to the significance of the findings. All that can be
said of the results of this study is that the 3.5% incidence
of gliomas among the 115 control animals is bizarre when
compared with the brain tumor incidence reported from
normative studies on the Charles River CD line of
Sprague-Dawley rats (Fitzgerald et al.: 0.7%; McKenzie and
Garner: 0.6%), and that the 2.5% incidence among the
aspartame-treated groups likewise lies well above the
normative figures.

Comment

The foregoing considerations leave the Board no choice
but to conclude that the data reported at the public hearing,
when taken at face value, do not rule out an oncogenic effect
of aspartame, and that, to the contrary, they appear to
suggest the possibility that aspartame, at least when
administered in the huge quantities employed in these
studies, may contribute to the development of brain tumors.

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The Board submits that the supranormal incidence of
brain tumors in the reported studies may be related to the
enforced consumption, throughout a lifetime, of quantities of
aspartame enormous enough to cause a sustained and profound
imbalance in the amino acid composition of blood plasma and
other tissue fluids. This raises the question whether
aspartame and other peptides might need to be tested for
oncogenicity by a protocol different from that employed in
the testing of compounds that are not, as aspartame is,
entirely composed of amino acids normally present in tissue
fluids. Such non-peptidic compounds might not so predictably
disrupt the amino acid balance when ingested in quantities
one-hundred or more times higher than any foreseeable human
use. Because of this consideration, the Board suggests that
experiments with aspartame doses closer to the projected
human consumption level (e.g., 100 and 200 mg/kg) be included
in future repetitions of the oncogenicity studies reported at
the hearing.

Conclusion Concerning Issue Number 2

The Board concludes that the reported data suggest the
possibility of an oncogenic effect of aspartame ingestion at
the extremely high level of 1000-6000 mg/kg throughout the
rat's lifetime. Yet, the exclusive use of such extreme
dosage in the screening of compounds consisting entirely of

amino acids normally present in blood plasma needs be
questioned, for the outcome might reflect no more than a
non-specific effect of an artificially maintained gross
imbalance in the amino acid composition of the tissue
fluids.

V. ISSUE NUMBER 3

>   Based on answers to the above
> questions,
>   (a) Should aspartame be allowed for
> use in foods, or, instead should approval
> of aspartame be withdrawn?
>   (b) If aspartame is allowed for use
> in foods, i.e., if its approval is not
> withdrawn, what conditions of use and
> labeling and label statements should be
> required, if any? 44 Fed. Reg. 31717.

On the basis of the conclusion concerning Issue Number
2, the Board concludes that approval of aspartame for use in
foods should be withheld at least until the question concern-
ing its possible oncogenic potential has been resolved by
further experiments. The Board has not been presented with
proof of a reasonable certainty that aspartame is safe for
use as a food additive under its intended conditions of use.

VI. ORDER

The foregoing constitutes the Board's findings of fact and conclusions of law.

Therefore, it is ORDERED that:

1. Approval of the food additive petition for aspartame (FAP 3A2885) be and it is hereby withdrawn.

2. The stay of the effectiveness of the regulation for aspartame, 21 CFR 172.804, is hereby vacated and the regulation revoked.

3. Pursuant to 21 CFR 12.125, exceptions to this Initial Decision must be received by the Hearing Clerk within 30 days; replies to exceptions must be received by the Hearing Clerk not more than 20 days thereafter. In the absence of the timely filing of exceptions, or of a review notice by the Commissioner under 21 CFR 12.125(f), this Initial Decision will become the Final Decision of the Commissioner upon the expiration of the date for filing for

appeal or review, and shall be effective upon publication
of a notice to that effect in the Federal Register.

Dated this ___30 th___ day of ___September___, 1980.

Walle J. H. Nauta, M.D., Ph.D.
Chairman

Peter W. Lampert, M.D.
Member

Vernon R. Young, Ph.D.
Member

ASPARTAME PUBLIC BOARD OF
INQUIRY

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