UNITED STATES OF AMERICA
BEFORE FEDERAL TRADE COMMISSION

In the Matter of	)	
NATURAL ORGANICS, INC., a corporation, and	)	DOCKET NO. 9294
GERALD A. KESSLER, individually and as an officer of the corporation.	)	

TO: The Honorable James P. Timony
Administrative Law Judge

COMPLAINT COUNSEL'S RENEWED MOTION TO LIMIT EXPERT WITNESSES

On February 16, Respondents named 14 experts as part of their case in chief, 12 of them claiming scientific expertise. Complaint counsel filed a motion on February 26 to limit the number of experts. Although hampered by the absence of expert reports, we argued that the experts' testimony inevitably would be cumulative and that time was of the essence.

Respondents then filed an Answer arguing our motion was not ripe for two principal reasons -- (1) "Because Respondents have not yet filed the expert reports [due March 14], Complaint Counsel have no way of knowing if any of the testimony to be provided by the experts is cumulative," and (2) Complaint counsel do not know "whether Respondents might delete any of the designated experts when the revised witness lists are exchanged later this month" [March 23].[1]

[1] Respondents' Response to Complaint Counsel's Motion to Limit Expert Witnesses, March 12, 2001, at 2.

On March 13, Your Honor entered an Order referring to the March 14th due date for expert reports and the March 23rd date for revised witness lists, and denying Complaint counsel's motion as not ripe. The Order stated that the denial was without prejudice to refile.

Those dates have now arrived, and we now know the answer:

1. Respondents have refused to delete *any* of the 14 witnesses;[2]

2. Respondents's expert reports contain grossly cumulative testimony:

   - *12 experts* address substantiation;
   - *All 12 experts* assess the same ingredient DMAE; [3]
   - *8 of these experts* assess the same ingredient phosphatidlyserine ("PS") or phosphatidylcholine (PC);[4]
   - *8 of these experts* opine on the nature of ADHD;[5]
   - *9 of these experts* recount observations from treating patients.[6]

There is nothing unique about this case that compels such duplication. Complaint counsel's expert, Dr. Eugene Arnold, *in one report* addressed all these issues -- ADHD, the science regarding every ingredient, testing protocols, and others.

The result of Respondents' approach is that Complaint counsel must take over 20

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[2] Letter from Wes Siegner, Jr. to Matthew Gold, March 23, 2001.

[3] William G. Crook, M.D., Leo Galland, M.D., Edward Hallowell, M.D., Richard Kunin, M.D., Richard J. Wurtman, M.D., Joseph A. Sanford, PhD., Osvaldo Re, M.D., Jerry Cott, Ph.D., Charles Gant, M.D/Ph.D., Parris M. Kidd, Ph.D., Peter R. Breggin, M.D., and Lester Packer, Ph.D..

[4] Cott; Crook; Galland; Gant; Hallowell; Kidd; Kunin, Packer.

[5] Breggin; Cott; Crook; Galland; Gant; Hallowell; Kunin; and Re.

[6] Breggin; Cott; Crook; Galland; Gant; Hallowell; Kidd, Kunin; and Re.

depositions of Respondents' witnesses by April 27. Complaint counsel are personally acquainted with the rigors of litigation, and that "there is never enough time." Here, it is the lack of justification for this burden, and waste of thousands of dollars, to which we object. [7] Respondents have not helped matters by their continued failure to supply certain critical expert witness materials and information, in violation of the Discovery Order. [8]

As will be shown, this is not a situation where Respondents assigned sub-topics to different experts. Under that scenario, each expert would add a piece of the puzzle rather than opine on the bottom line. Instead, Respondents' approach was totally cumulative -- they gave largely duplicative material to all 12 witnesses in the hope *they all* would opine on whether Respondents' claims were substantiated. And each witness somehow did, despite Respondents' seeming contention that no one can reach a bottom line without all these supposed disciplines.

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[7] Complaint counsel is grateful for the extension of time from April 13 to April 27. (Second Revised Scheduling Order, March 27, 2001). We respectfully submit that we still face inordinate time and monetary burdens if Respondents' list of 14 experts is allowed to stand. Our 20-plus depositions -- not including ones we must defend -- would have to take place in less than 20 business days, counting from Monday, March 2. The fact that we now face a compressed schedule for finishing both expert and fact witnesses must be laid at Respondents' doorstep. In letters of February 27 and March 15, as well as telephone calls, we repeatedly argued that if Respondents wished to name so many expert witnesses, that we had to start reserving open dates if we were to have any hope of meeting the discovery deadline. Respondents repeatedly refused and that process is beginning only now.

[8] *See*, Complaint Counsel's Motion to Limit Expert Witnesses, at 5. Respondents, though in untimely fashion, have since provided some additional materials, but not all. The Discovery Order, for example, requires that parties to identify "all prior cases in which the expert has testified or has been deposed." Respondents have viewed it as sufficient to state, for example, that "Dr. Wurtman has been deposed two times: approximately ten years ago in a case involving L-triptophan and more recently in a case involving phentermine." Letter from A. Wes Siegner, Jr. to Matthew Gold, March 12, 2001. Respondents offered similar generalizations for at least 6 other experts (*e.g.*, "Dr. Sanford has been deposed in two personal injury cases that settled."). This gives us no information we can use to retrieve the case information on our own.

Either that assumption is untrue, or you really do have 12 experts "going over the same ground."[9]

In sum, Respondents' approach is nothing but a numbers game at odds with the case law condemning cumulative testimony. *Leefe v. Air Logistics, Inc.*, 876 F.2d 409, 411 (5th Cir. 1989)(the rationale for excluding cumulative expert testimony is to "discourage attorneys from parading additional experts before the court in the hope that the added testimony will improve on some element of the testimony by the principal expert.") We respectfully request that Your Honor place reasonable limitations on Respondents' selection of experts.[10]

Specifically, we request that Your Honor direct Respondents to limit themselves to five experts, based on these generous assumptions -- that they may need 2 experts to discuss the effects of DMAE and/or other product ingredients; one expert to discuss ADHD; one consumer perception expert (Ivan Preston); and one FDA law expert (Eugene Lambert). If Respondents choose experts who discuss multiple topics in their reports (*e.g.*, DMAE, PS, and ADHD) -- and many do -- so be it. There can be cumulative testimony to that extent. Respondents could

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[9] We exclude from our analysis Dr. Ivan Preston's Report and Mr. Eugene Lambert's reports on the grounds that they address consumer perception and FDA law issues, respectively. These subject matters do not overlap significantly with the other experts' proposed testimony. Our own second expert, Dr. Eric Murphy, falls in the same category.

[10] Commission Rule 3.43(b) provides: "Evidence, even if relevant, may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of issues, or if the evidence would be misleading, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." The Commission included this language in Rule 3.43(b) for the first time in 1996 when it amended its rules of practice for adjudicatory proceedings. At that time, the Commission stated: "The amended rule is intended to make clearer to litigants that the ALJ is empowered to exclude unduly repetitious, cumulative, and marginally relevant materials that merely burden the record and delay the trial. This clarification is intended to enhance the ALJ's ability to assemble a concise and manageable record." 61. F.R. 50639, 50644 (Sept. 26, 1996).

choose experts according to the foregoing formula, or any other five experts they wish.[11]

Complaint counsel also respectfully request that Your Honor shorten to 5 days the time for Respondents to answer this Renewed Motion.

I. RESPONDENTS' "NUMBERS GAME" APPROACH MISCONSTRUES THE ROLE OF EXPERT TESTIMONY

Complaint counsel continue to believe that burdening our discovery efforts is one motivation for Respondents' approach. However, it appears now that Respondents also believe that determining FTC advertising substantiation is somehow a "numbers game":

> Complaint counsel have offered no stipulations regarding Respondents' experts' testimony. Thus, for instance, *we are left to guess whether Complaint Counsel will agree that if a certain number of experts conclude that Respondents' advertisements were substantiated, Respondents will have thereby established their defense to the Complaint. Indeed, we suspect that no matter how many experts Respondents proffer, Complaint counsel will contend that we have not shown that the advertisements were substantiated.* Thus, it is quite conceivable that there will be some necessary overlap between the testimony of some of Respondents' experts. (Emphasis added)[12]

As set forth below, we recommend that Your Honor reject Respondents' premise and require them to make a reasonable selection among their experts. "Counting experts" is a game both sides could play -- perhaps Complaint counsel to greater effect in this instance. However, this approach is defective on several grounds. First, it misconstrues the role of the expert in litigation -- to aid the fact-finder in assessing the body of literature, tests, and other materials through informed opinion. One good expert can

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[11] Our review of the actual expert reports indicates to us that our earlier Motion to Limit Experts was too generous in stating that six experts possibly could be justified. It was a surprise even to us that Respondents named fully twelve experts to opine on the effectiveness of DMAE.

[12] Respondents' Response to Complaint Counsel's Motion to Limit Expert Witnesses, at 6 - 7.

perform this task as well as one hundred.

Second, the counting- experts approach virtually invites future wars of attrition in FTC advertising cases. As was done here, Respondents could routinely impose huge burdens on Commission staff simply by naming large numbers of experts and making no selection at the pre-trial discovery stage. The Commission, in amending the Part III Rules of Practice in 1996, sent a clear signal that such tactics should not be tolerated:

> 6. Rule 3.31(b)(1) [.... .] is being amended and predesignated as 3.31(c)(1) to strengthen the ALAS' authority to prevent abusive discovery tactics by limiting the frequency or extent of discovery under certain conditions (e.g., when it would be cumulative or duplicative) . . . . [13]

Obviously, parties can generate needless discovery not only by issuing such discovery themselves, but also by imposing needless discovery on the other side. Respondents' contention that we are only *imagining* a duty to conduct depositions of its experts is facially absurd, as is their suggestion that we conduct all expert depositions by telephone.[14]

II. ANALYSIS OF RESPONDENTS' EXPERT REPORTS AND PROPOSED LIMITING PRINCIPLES

We recognize that there is no magic number of appropriate experts in any litigation. "One more expert" possibly can add some value. However, the dictates against cumulative testimony require parties to make choices. Respondents should not be permitted free rein based

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[13] 61 Fed. Reg. 50640, at 50643 (September 26, 1996).

[14] Respondents make the painfully obvious point that we have no *legal* duty to conduct depositions at all ("Complaint counsel are clearly confused") and state -- "Moreover, this argument conveniently avoids the fact that even if Complaint Counsel desire to depose each of the experts, they could do so by telephone deposition." Respondents' Response, at 5. Respondents' counsel would be courting a malpractice suit if they took their own advice. There is a considerable distinction between lesser fact witnesses and experts in this regard.

on the conclusory statement that "we have put together a highly-qualified panel of experts who, collectively, will be prepared to stick a fatal dagger in the underpinnings of the Complaint." Respondents' Response, at 7.[15]

Complaint counsel, although tempted to comment on the merits of Respondents' expert reports, will confine our analysis to identifying overlapping subject matters therein. We attach Respondents' expert reports in alphabetical order in Attachment A. For comparison purposes, we also attach Dr. Arnold's report as Attachment B. A chart summarizing the subject matters addressed in Respondents' reports is found in Attachment C.

A. There are No Unique Aspects of the Case That Warrant Respondents Using a "Panel" of Experts

Dr. Eugene Arnold's report refutes the idea that there is anything particularly unique about this case that warrants a "panel" of experts for Respondents. He addresses all the subjects needed to evaluate whether Respondents possess substantiation for their claims -- (1) the nature of Attention Deficit Hyperactivity Disorder ("ADHD" or "ADD"); (2) the scientific literature, published tests, and theoretical bases for any claimed effect of PediActive A.D.D. and its individual ingredients; (3) how clinical practice experience should be evaluated; and, *inter alia*, (5) what level of testing and other scientific evidence one reasonably can expect with respect to a product of this nature. Dr. Arnold speaks from several realms of expertise, most notably

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[15] Respondents' characterization in their Statement of the Case adds no more logic – simply touting "the array of disciplines represented, including; nutritional biochemistry and neuroscience; cellular and developmental biology; child and general psychiatry; pediatric, allergy, and preventive medicine; clinical psychology; physiology; pharmacology, neurolopharmacology, and pharmocokinetics," and proclaiming that "Included among Respondents' scientific expert witnesses are eight medical doctors, four of whom have used either one or both of the dietary ingredients contained in PediActive A.D.D. . . .." Respondents' Statement of the Case, at 12 (filed March 23, 2001).

psychiatry and his treatment of ADHD specifically; years of conducting clinical research; and his ability to interpret scientific evidence.

Complaint counsel understand that Respondents need not mirror our approach. There are times when parties may wish to delegate sub-issues to experts from different disciplines. A corroborating witness might even be appropriate in limited circumstances. That is not the approach Respondents pursued.

B. Respondents' Expert Reports are Facially Cumulative

Complaint counsel have prepared a simple chart of the basic subject areas and authorities that Respondents' substantiation experts mention in their reports (Attachment C). It is undeniable that Respondents have assigned the "same homework" to 12 different people.

Cumulative testimony regarding the possible effects of DMAE: Twelve experts rendered an opinion on the effects of DMAE. Respondents cannot pretend that this overlap was by accident:

- Counsel gave every expert the same 1975 Lewis and Young study to at least 10 experts, and perhaps to all 12. We can expect that most or all of them will address the study in their testimony.[16]
- Counsel gave numerous other publications to multiple experts;[17]

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[16] The 1975 Lewis & Young study is one of the few relevant double-blind, placebo-controlled studies of DMAE that exists. There undoubtedly will be much focus in the trial on whether that study was well constructed, used relevant dosages, or was probative in other respects. Our only doubt as to whether two experts were given this report is that (1) the list of materials sent for Dr. Breggin does not include the item (though he cites it profusely in his report) and (2) Respondents simply provided no list of materials at all with respect to Dr. Kunin.

[17] For example, the NAS/NRC Deanol Panel review (10 experts); Oettinger (9 experts); Lewis & Lewis (9 experts); Re (8 experts); Geller (10 experts); Murphree (10 experts). There are

- Even the experts who gave the most opaque, cursory reports purported to review the above DMAE literature (*e.g.*, Hallowell, Kunin).

At least 8 experts purport to testify about the potential effects of Phosphatidylserine (PS) and Phosphatidylcholine (PC): The most prominent secondary ingredients in PediActive A.D.D. are PS and PC. Fully 8 experts purport to have opinions on whether those ingredients enhance brain function or otherwise have sufficient effects to substantiate Respondents' claims.

At least 8 experts render opinions about the nature of ADHD and its symptoms: We have not only multiple psychiatrists testifying about the nature of ADHD (Breggin, Hallowell, Kunin), but also pharmacologists (Cott), pediatricians (Crook), and others.

At least 9 experts address patient observations in private practice: At least nine of Respondents' experts either recount observations in their own practices, or refer to uncontrolled observations in other persons' practices. Staff recognizes that in a case such as this, it may be instructive to consider lessons learned by healthcare professionals in actually treating children with respect to ADHD symptoms. However, any attempts by Respondents' experts to generalize from their uncontrolled patient observations to the population at large has limited value and there is no justification for multiple experts on this topic. "Anecdotal evidence, such as testimonials by satisfied patients or statements by doctors that, based on their experience, they 'believe' a drug is effective do not constitute adequate and well-controlled investigations and cannot, therefore, provide substantial evidence of effectiveness." *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, at 618-19, 629-30 (1973).

For the above reasons, we submit that Respondents' expert reports fit every reasonable

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numerous other core documents that went to multiple experts.

definition of cumulative testimony. There is ample case law supporting reasonable limitations on such testimony.[18]

III. RECOMMENDATION

Counsel respectfully requests that Your Honor limit Respondents to five experts. Permitting five experts, versus our two, is more than fair. That number accepts any contention by Respondents that evaluations of DMAE and PS/PC require different expertise (2 experts); that a separate expert may be needed to opine on the nature of ADHD; and that separate experts are needed to address FDA law and consumer perception issues. However, Respondents could ignore these categories and name any 5 experts they wish. We respectfully request that Your

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[18] We refer Your Honor to case law cited in our first Motion to Limit Experts (February 26, 2001), at 14 - 15, including but not limited to *Davis v. Mason County,* 927 F.2d 1473, 1484 (9th Cir.), *cert denied,* 502 U.S. 899 (1991)(affirming trial court's exclusion of expert testimony as cumulative where excluded testimony would have been on the "same topic" as another expert's testimony); *Elwood v. Pina,* 815 F.2d 173, 178 (1st Cir. 1987) (citation omitted)("Evidence is cumulative if repetitive, and if 'the small increment of probability it adds may not warrant the time in introducing it.'"); *Upsher-Smith Laboratories, Inc. v. Mylan Laboratories, Inc.*, 944 F. Supp. 1411, 1440 (D. Minn. 1996) (court 'may limit or exclude expert testimony which is cumulative."); *Aetna Cas. & Sur. Co. v. Guynes*, 713 F.2d 1187, 1193 (5th Cir. 1983); *Rios v. Bigler*, 847 F. Supp. 1538, 1550 (D. Kan. 1994), *aff'd*, 67 F. 3d 1543 (10th Cir. 1995); *Leefe v. Air Logistics, Inc.*, 876 F.2d 409, 411 (5th Cir. 1989); *Adalman v. Baker, Watts & Co.*, 807 F.2d 359, 370 (4th Cir. 1986).

Honor enter the attached Order to that effect.

We also respectfully request that Your Honor shorten to 5 days the time for Respondents to answer this Renewed Motion.

Respectfully submitted,

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Dated: March 28, 2001

UNITED STATES OF AMERICA
BEFORE FEDERAL TRADE COMMISSION

In the Matter of	)	
NATURAL ORGANICS, INC., a corporation, and	)	DOCKET NO. 9294
GERALD A. KESSLER, individually and as an officer of the corporation.	)	

TO: The Honorable James P. Timony
Administrative Law Judge

ORDER GRANTING COMPLAINT COUNSEL'S MOTION TO LIMIT EXPERT WITNESSES

Upon consideration of Complaint Counsel's Motion to Limit Expert Witnesses and Renewed Motion, and Respondents' Objections thereto:

IT IS HEREBY ORDERED that Complaint Counsel's Motion is granted.

IT IS FURTHER ORDERED that within five (5) days of the date of this Order, Respondents shall provide a new expert witness list to Complaint Counsel. Such list shall be limited to five names.

James P. Timony
Administrative Law Judge

Dated:

CERTIFICATE OF SERVICE

This certifies that a copy of Complaint Counsel's Renewed Motion to Limit Expert Witnesses was served by facsimile and Federal Express on March 28, 2001, on the following:

John R. Fleder, Esq.
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In addition, two copies were served by personal delivery on:

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Peter R. Breggin, M.D.

I. Purpose

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler.

This is a report that will focus on one of the ingredients in Pedi-Active A.D.D. I expect to have the opportunity to review additional materials and to develop a further analysis of other ingredients.

II. The FTC Guidance

A. The Guidelines

The following guidance is taken from the FTC "An Advertising Guide for Industry" under the heading of "The Amount of Substantiation that Experts in the Field Believe is Reasonable." The FTC states in part, "In making this determination, the FTC gives great weight to accepted norms in the relevant fields of research and consults with experts from a wide variety of disciplines, including those with experience in botanicals and traditional medicines." It goes on to say:

> The FTC typically requires claims about efficacy of safety of dietary supplements to be supported with "competent and reliable scientific evidence," defined in FTC cases as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."

The above are but some of the guidelines that the FTC gives for substantiation.

B. Application of the Guidelines For This Report

Based on these guidelines, the following conclusions seem apparent:

(1) These FTC criteria are far less stringent than the standards that the FDA uses for approving drugs;

(2) A finding of "possibly effective" by the National Academy of Sciences (NAS) in 1970 based on much more limited data than is now available and based on the far more stringent FDA requirements should, in the absence of serious adverse effects or toxicity, meet or exceed the above requirements of the FTC for a dietary supplement;

(3) A dietary supplement whose effectiveness has been demonstrated to the satisfaction of well-known scientists and researchers in double-blind, placebo-controlled studies published in reputable journals, as well as in a variety of other studies, and that has the support of numerous well-known experts, should meet the FTC requirements;

(4) A substance which has no known serious toxicity, and which meets the above standards that I have described, should meet the FTC requirements.

These above considerations reflect the kind of criteria that this will report will bring to bear on the subject.

III. Background of the Expert

I am a psychiatrist in private practice in Bethesda, Maryland (since 1968) and the director of the International Center for the Study of Psychiatry and Psychology. I am also the founder and co-editor of the peer-reviewed journal, Ethical Human Sciences and Services (Springer Publishing Company), and am on the editorial board of several peer-reviewed journals, including the International Journal of Risk and Safety in Medicine. I have written, lectured, and consulted extensively on the subject of stimulant drugs and ADHD (see bibliography at the end of the report).

Recently I was selected by the National Institutes of Health (NIH) to be the expert on adverse drug effects in children at the November 1998 Consensus Development Conference on the Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (Breggin, 1998b). My presentation also included an analysis of the mechanism of action of stimulant drugs.
As a result of my research and professional experience, I have considerable expertise in the FDA drug approval process, in the use and evaluation of stimulant drugs in children, and in the safety of FDA-regulated products in general.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

I have assumed for the purpose of my review that the FTC is correct in its assertion that Natural Organics' advertisements include claims that the dietary supplement Pedi-Active A.D.D. will improve the attention span and scholastic performance of children who have ADHD or who have difficulty focusing on school work, and will treat or mitigate ADHD-like behaviors.

It is my opinion that there is sufficient scientific evidence in the literature that supports these claims for the main active ingredient, DMAE or deanol. Formerly marketed as Deaner by Riker Laboratories, deanol is 2-dimethylamino-ethanol bitartrate (DMAE). The most cogent data is found in double-blind placebo-controlled studies (such as Lewis and Young, 1975). It is also my opinion that the product, when used as suggested by the manufacturer, does not raise any significant safety issues.

IV. Analysis of Issues, Scientific Studies and Data

A. Controversial Nature of ADHD

Considerable controversy surrounds the diagnosis of ADHD, including its validity (Armstrong, 1995; Barbarin and Soler, 1993; Breggin, 1998a; Breggin and Breggin, 1996; Carey, 1998; McGuinness, 1989; National Institutes of Health, 1998a&b). Because of the controversy surrounding the concept of ADHD, I will refer to ADHD-like symptoms without endorsing the concept of ADHD as a valid disorder. The controversial nature of ADHD as a disorder, in my medical opinion, makes the use of varied non-medical and nutritional approaches more justified. It also lessons the urgency to emphasize medical interventions, such as stimulant medication.

There are many bases for the controversy surrounding ADHD as a disorder.

The first and therefore most "powerful" behavioral items under the categories of hyperactivity, impulsivity, and inattention in the Diagnostic and Statistical Manual of Mental Disorders, IV (DSM-IV) (American Psychiatric Association, 1994) are the following: "Often fidgets with hands or feet or squirms in seat," "Often blurts out answers before questions have been completed," and "Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities."

As indicated by the above symptoms, ADHD is simply a list of highly varied behaviors that can be disruptive in classrooms and other settings. Even when extreme, these behaviors have no common biological origin but can be caused by a variety of stresses, including overly large classrooms, poor teaching, poor discipline at home, emotional abuse, and nutritional problems. They can also be the result of normal childhood behavior.

Undermining the concept of a biological disorder, the DSM-IV itself acknowledges that ADHD-like behaviors tend to disappear when the child is consistently disciplined, appropriately entertained, or engaged in a one-to-one relationship with an adult, and second, that the behaviors often occur or worsen in response to boring, monotonous tasks.

In short, the DSM-IV establishes that ADHD is a "disorder" that has little or nothing in common with genuine physical disorders or diseases. It is a collection of unrelated behaviors that disrupt classrooms, and it often disappears when the child receives proper discipline and attention. Multiple sclerosis, cerebral palsy, genetic mental retardation, and other genuine neurological disorders would not so readily disappear under improved environmental circumstances. Furthermore, these genuine biological disorders produce symptoms that can be understood as a medical syndrome—an array of biologically determined symptoms.

Given the varied behavior that falls within the DSM-IV diagnosis for ADHD, as well as the almost infinite number of causative factors from inadequate teaching and poor nutrition to normal childhood behaviors, it is not surprising that no single method of improving ADHD-like will be effective for all children diagnosed with ADHD. This is true for nutritional approaches as well as drug and psychiatric approaches.

From my review of the scientific literature relating to DMAE, it is my medical opinion that the claims that the FTC alleges are made for this product are substantiated in the scientific literature by methods similar to or the same as those used for clinical drug trials.

B. Example of a Controlled Clinical Trial that Substantiates the Claims for Pedi-Active A.D.D.

I have reviewed a number of studies of deanol or DMAE. I have reviewed these studies in the context of my knowledge of the database that exists for other ADHD treatments, including methylphenidate.

This report will focus on one study that substantiates that the DMAE component of Pedi-Active A.D.D. by itself can have the effects that the FTC alleges the advertising for this product claims. The study by Lewis and Young (1975), was conducted according to the basic canons required for a clinical drug trial, including a careful description of methodology, varied screening and evaluation methods, a double-blind procedure, a placebo control, and a comparison active control group taking methylphenidate. Although the FDA later rejected this study as evidence of effectiveness under that agency's more stringent standards for approving drugs, it appears to have been a close call. The study (and several others) certainly meets the criteria of the FTC guidance. Here are some salient points about the study:

(1) In the statistical analysis, while methylphenidate produced a better result on the WISC, DMAE in fact produced a better result on the Bender-Gestalt (p. 537).

(2) Parent or teacher ratings are often viewed as the gold standard in ADHD research. Deanol and methylphenidate produced equal improvement in the children on the parent behavioral rating scale

(3) Even if DMAE were interpreted to be somewhat less effective than methylphenidate in this study, it would still be

an approach to ADHD-related symptoms. Indeed, in this study DMAE produced no adverse effects.

(4) The dose of DMAE provided by Pedi-Active A.D.D.--300-400 mg per day versus 500 mg per day in the Lewis and Young study--is not a significant difference for a nutritional product. Since DMAE is non-toxic in this dose range, it would be safe to increase the recommended dose to 500 mg.

(5) The study duration was three months, making it one of the longer-term double-blind placebo-controlled clinical trials involving a treatment for ADHD or ADHD-like symptoms.

(6) The study compared a relatively small dose of DMAE to a relatively large dose of methylphenidate. In other words, a relatively small and harmless dose of DMAE was found statistically comparable in therapeutic effect to a relatively large dose of methylphenidate.

(7) Unlike most studies of stimulant drugs for ADHD-like behaviors, the Lewis and Young study used multiple objective tests for evaluating the effects.

(8) Unlike most studies of stimulant drugs for ADHD-like behaviors, the study demonstrated improvement in areas of mental functioning as well as behavior for both deanol and methylphenidate.

(9) In comparison to most studies of stimulants for treating ADHD-like behaviors, intensive physical and mental screening tests were carried out on the children who participated in the study. Therefore, within the limits of the ability to screen for ADHD-like behaviors, the children chosen to participate in the Lewis and Young study were well-screened.

(10) Finally, the senior author of this study, James Lewis, was a physician and researcher at the University of Colorado Medical Center, the study was sponsored in part by a Public Health

Service Grant (accounting in part for its high standards), and the study was published in a well-established peer-reviewed scientific journal.

The Lewis and Young study, alone or in combination with supporting data from other studies, is sufficient to provide scientific substantiation for the claims for a product such as Pedi-Active A.D.D. that is a dietary supplement with no serious safety issues.

C. Additional Relevant Studies

Here are some of the additional studies and professional publications that have lent support to the use of deanol for the treatment of ADHD-like behaviors. In the case of rising doses, the listed doses are for the final period of the study:

Coleman, N., Dexheimer, P., DiMascio, A., Redman, W., and Finnerty, R. (1976). Double-blind placebo-controlled study of 50 children ages 6-12 with 500 mg for 12 weeks.

DiMascio and Finnerty (undated, unpublished FDA approval study). Double-blind placebo-controlled study of 50 children age 6-12 with 500 mg daily for twelve weeks.

Fields, E. M. (1961). Clinical study of 100 subjects age 2-19 years with 100 mg daily for ten months.

Geller, S. (1960). Double-blind, placebo-controlled study of 75 children ages 5-12 for three months with 500 mg daily.

Lewis and Lewis. (unpublished, undated for FDA approval). A double-blind placebo-controlled study of 18 children age 6-10 given 500 mg daily for one month.

Lewis and Young (1975). See section IV-B above analysis.

Oettinger, Jr. (1958) Clinical study of 108 children, 74 evaluated, with 20-200 mg per day for up to more than 9 months.

Oettinger, Jr. (1977). Review.

Many of these publications were by well-known researchers whose professional careers lie in the field of drug evaluation rather than nutritional supplement evaluation. Many of the studies were published in established journals devoted to medical and pharmacological research rather than to nutrition. In other words, the researchers and the journals were not necessarily advocates of nutritional supplements, but their work supported the efficacy and safety of deanol.

In addition, a number of other studies were reviewed for the FDA approval process but are not yet available in their entirety.

V. Results of the Evaluation of the Panel on Psychiatric Drugs

In 1958, deanol under the trade name Deaner was originally approved by the FDA for the treatment of (1) "learning problems," (2) "behavioral problems—hyperkinetic behavior problem syndrome," and (3) various combinations of the above. The initial recommended dose was 300 mg per day with the suggestion of reducing it to 100 mg per day after a satisfactory result had been achieved. The agent was considered a mild stimulant.

At the time the FDA approved this original label, proofs of safety but not efficacy were required. In 1962 the Harris-Kefauver amendments established new criteria that, in addition to safety, manufacturers supply evidence for claims of efficacy for drugs approved between 1938 and 1962.

Under the new legislation, the FDA began a re-evaluation of Deaner for efficacy. Its safety was never in doubt. The FDA had empowered the National Academy of Sciences—National Research Council to carry out these re-evaluations. Deanol was evaluated as a New Drug Application (NDA) by the Panel on Psychiatric Drugs (undated, circa 1970).

The Panel on Psychiatric Drugs determined that deanol was "possibly effective" for the treatment of ADHD-like symptoms using standards required for FDA approval of a psychiatric drug, such as a stimulant, for the same purpose. Deaner specifically was found "possibly effective" for "learning problems," "hyperkinetic behavior syndrome," "varying combinations of both the above," "underachievers," "reading and speech difficulties," "impaired motor coordination," "hyperactive, impulsive/compulsive behavior often described as asocial, antisocial, delinquent, stimulus-governed." This broad spectrum of possibly effective uses covers the range of claims attributed to Natural Organics.

The panel also sought the opinion of two independent consultants. One found deanol to be "effective" and the other found it to be "possibly effective." The consultant who evaluated deanol as "effective" specifically described its effectiveness for behaviors that are now diagnosed as ADHD, including "Hyperkinetic Behavior Syndrome." The consultant included learning disorders in this syndrome.

The committee, including its two consultants, concluded the evaluation without benefit of the Lewis and Young study which had not yet been published.

It is important to emphasize that the standards applied to the evaluation were those used for drug approval by the FDA. Based on the report of the Panel on Psychiatric Drugs, the ingredient deanol fulfilled the claims made by Pedi-Active A.D.D. at the level required for a nutritional supplement under the FTC standards for substantiation.

The Food and Drug Administration again considered Deaner (deanol) in a report on May 24, 1983 and once again refused to elevate the substance to a status above "possibly effective." They made three specific criticisms of Lewis and Young study. First, that the selection criteria were "relatively loose." Second, in the same vein, they felt that the selection method did not insure that comparability of the control groups and the deanol group. In regard to these two criticisms, the groups were randomly assigned, and most of the children suffered from hyperactivity. The admittedly loose criteria were certainly within the category of ADHD which is itself rather loose, spanning a widely divergent group of behaviors under the vague categories of inattention, impulsivity, and hyperactivity. To the extent the criteria were relatively loose, that in fact reflects the criteria for ADHD as defined to this very day. In addition, a number of screening tests were employed. The FDA's third complaint was that it was unknown whether or not the children received concomitant drugs. As I have documented, Prozac and other drugs have been approved while the subjects were taking psychoactive concomitant drugs (Breggin, 1997). The FDA also failed to take into account that the effectiveness of the stimulants in the same study adds some validity to the original selection process.

Although the FDA saw fit not to approve the Lewis and Young study, the study was published by a respected researcher in an established journal and offers valid scientific evidence for the effectiveness of deanol. Although the FDA ultimately rejected Deaner as only <u>possibly effective</u>, overall, the deliberations of the FDA committees confirmed that a number of authorities and several studies have found deanol effective or possibly effective for ADHD-like symptoms including hyperactivity and learning problems. This I believe should be sufficient to justify the claims made for the nutritional supplement.

VI. Bases for Opinions

I have reviewed studies and other information that were provided to me by counsel to Natural Organics, and a list of those materials is provided (Appendix A). I have also reviewed the report of Dr. Eugene Arnold and many of the studies and much of the information he has cited in his report and provided with his report. In addition, I have conducted my own research into the issues relating to the substantiation of the Pedi-Active A.D.D. and have relied on my own publications and those of others on ADHD issues. A series of my peer-reviewed articles (Breggin, 1999a,b&c) (Breggin 1999c is attached as Appendix B) offers extensive bibliographies of those materials, which includes numerous textbooks and other sources. Although it is not practical to provide copies of all of these materials, I would be happy to provide copies of any relevant information that is requested.

VII. Conclusion

There is scientific evidence in the literature from numerous sources, including double - blind placebo-controlled studies, for the efficacy of deanol (DMAE) for behavioral problems in children including ADHD-like behaviors. Many reputable scientists have published reports in highly regarded journals that support the use of deanol for these purposes. Indeed, one of two outside consultants in the FDA/NSA deliberations considered deanol "effective" for the treatment of ADHD-like symptoms while the other consultant and the FDA itself found deanol "possibly effective" for these purposes.

There is general agreement among experts that deanol lacks serious adverse effects. While I recommend psychological and educational approaches in my psychiatric practice rather than nutritional or pharmacological ones, based on the scientific research summarized in this report I recommend that physicians and parents try deanol (including Pedi-Active A.D.D.) before going ahead with prescribed stimulants such as methylphenidate or amphetamine.

Using scientific criteria similar to those used as the basis for the treatment of ADHD-like behaviors with prescribed stimulants, the DMAE in Pedi-Active A.D.D. provides a relatively safe and potentially effective treatment for ADHD and ADHD-like behaviors. Therefore, it is my opinion that Pedi-Active A.D.D. should be allowed to remain on the market with the advertising that the FTC has challenged in this case.

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Panel on Psychiatric Drugs. (undated, circa 1970). Evaluation of the NDA for Deaner (NDA 11417).

Appendix A: List of materials provided by attorney.

Appendix B: Breggin (1999c), "Psychostimulants in the treatment of children diagnosed with ADHD: Risks and mechanism of action."

Materials Sent to Dr. Peter Breggin

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.
3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)
4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.
5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application
6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)
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20. Moderators and Mediators of Treatment Response for Children with Attention-Deficit/Hyperactivity Disorder, Vol. 56, Dec. 1999, pp. 1088 – 1096.

21. Arnold L, et al. Potential Link Between Dietary Intake of Fatty Acids and Behavior: Pilot Exploration of Serum Lipids in Attention-Deficit Hyperactivity Disorder, *J. Child and Adolescent Psychopharmacology*, Vol. 4, No. 3, 1994, pp. 171-182.

22. Methylphenidate vs. amphetamine: Comparative review, *J. of Attention Disorders*, Vol. 3, No. 4, Jan. 2000, pp. 200-211.

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case, In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Jerry Cott, Ph.D.

I. Introduction

I have been asked to provide an expert opinion regarding the scientific substantiation for advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I am a Ph.D. pharmacologist with 25 years experience in psychotherapeutic drug development, including eight years at three pharmaceutical companies, four years at the Food and Drug Administration (FDA), and nine years at the National Institute of Mental Health as Chief of the Psychopharmacology Research Program. Presently, I have my own consulting firm.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

I have assumed for the purpose of my review that the FTC is correct in its assertion that Natural Organics's advertisements include claims that the dietary supplement Pedi-Active A.D.D. will improve the attention span and scholastic performance of children who have ADHD or who have difficulty focusing on school work, and will treat or mitigate ADHD or its symptoms. It is my opinion that these claims are substantiated by scientific data. As a scientific expert in this proceeding, however, I am not qualified to render any opinion as to what the advertisements mean, or whether Natural Organics' advertisements actually make the claims as the FTC has alleged. It is also my opinion that the product does not raise any safety issues.

My opinion is based on materials provided to me by counsel to Natural Organics, additional studies included as references to this report and my general scientific knowledge in this field.

II. Analysis of Issues, Scientific Studies and Data

A. Characterization of ADHD

Attention Deficit Hyperactivity Disorder, ADHD or just ADD, is generally characterized by developmentally inappropriate behaviors. Children with ADHD have difficulty paying attention, listening to instructions, and completing tasks. They have poor impulse control and/or excessive motor activity; they often fidget, squirm, and interrupt others. These behaviors may affect school performance, family relationships, and social interactions with peers. The cause of ADHD is unknown, but is believed to be complex, with biological, environmental and nutritional components.

The understanding of what is now classified as ADHD has been evolving for several decades, but not without a great deal of controversy. During this period, methylphenidate was approved by the FDA for the treatment of "minimal brain dysfunction" (and associated behavioral problems in children), which today would include symptoms classified as ADHD.

ADHD is highly inhomogeneous in the biological sense, and although classed as a disorder it amounts to hardly more than an assemblage of symptom clusters. Its etiology also is far from homogeneous, with many likely contributory factors. Certainly some of these etiological factors generate symptomatologies that closely resemble ADHD. Among these are sensitivities to food additives, intolerances to foods, nutrient deficiencies and imbalances, and heavy metal toxicity.

B. Clinical and Scientific Data That Substantiate Advertising Claims for Pedi-Active A.D.D.

DEANOL BACKGROUND

Deanol (2-dimethylaminoethanol; DMAE) was marketed in the United States from 1958 until 1983 by Riker Laboratories (now 3M Pharmaceuticals). It was originally thought to increase levels of acetylcholine in the brain. It does inhibit the breakdown of choline by inhibiting choline oxidase, however, which might result in increased levels of this acetylcholine precursor (Lohr and Acara, 1990). It may also have direct regulatory functions apart from its role as a precursor (Kiss and Crilly, 1996). Also, it has been shown to enhance production of polyunsaturated phospatidylcholines (Alvaro et al., 1989) that are crucial for normal neuronal function. The mechanism appears to be through stimulation of the microsomal enzyme, phosphatidylethanolamine *N*-methyltransferase. It is also incorporated directly into phosphatidyldeanol (Miyazaki et al., 1976; Ansell and Spanner, 1979; Dainous and Kanfer, 1988), though it appears to be rapidly methylated by the liver to phosphatidylcholine (lecithin) (Ansell, 1981; Alvaro et al., 1989). The remarkable retention of C^{14}-labeled deanol in the brain (compared with that of choline) (Groth et al., 1958) is consistent with its rapid incorporation into membrane phospholipids.

Based on a safety review, the indications that were approved by the FDA and stated in the labeling included:

1. Learning problems – learning deficit of that usually associated with apparent level of intelligence, including: I.Q. Reading Difficulties. Shortened attention span.
2. Behavior problems – hyperkinetic behavior problem syndrome characterized by distractibility, motor disinhibition, dissociation, and perseveration.
3. Or, as more frequently encountered, hyperkinetic behavior and learning disorders incorporating varying combinations of both of the above. Underachievers. Reading and speech difficulties. Impaired motor coordination. Hyperactive. Impulsive/compulsive behavior. Often described as asocial, antisocial, delinquent, stimulus-governed.

After the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (FDC Act), the FDA requested additional information regarding efficacy for deanol as well as for all drugs approved between 1938 and 1963. FDA requested help from the National Academy of Sciences (NAS)/National Research Council (NRC) for this review process. In a ten-page report, the panel gave the views of two "consultants" who evaluated the clinical data for deanol. It is of interest that the two consultants were apparently given two different sets of clinical trials to review. The first reviewer who said it was "effective" listed eight studies that convinced him (NDA p. 1578-1581). The second reviewer listed ten studies (NDA p. 1583), and while there was overlap, the second reviewer did not refer to the following three double-blind, controlled trials that the first one did:

Fleming, J.W., Orlando, R. Effect of deanol on attention in the mentally retarded: A reaction time method. J. New Drugs, July/August, p. 239, 1962.

Jacobs, J. A controlled trial of deaner and a placebo in mentally defective children. Brit. J. Clin. Prac. 192, February 1965, p. 77.

Knobel, M., Abramovsky H. El 2-Dimethylaminoethanol in behavioral problems of children. Semana Med, 119(24), September 16, 1961, p. 939. [Spanish]

Reviewer 1: Bostock 1962; Clausen 1960; Fields 1961; Fleming 1962; Geller1960; Huddleston 1961; Jacobs 1965; Knodel 1961

Reviewer 2: Bostock 1962; Clausen 1960; Eominium(?); Fields 1961; Geller1960; Huddleston 1961; Kugel 1963; Oettinger 1958; Rimland 1964; Tobias 1959.

Thus, these controlled trials were not seen by the second reviewer who found the data "possibly effective." A review of the literature from this time period shows that there were other additional trials that were also not reviewed by the NAS panel. The panel as a whole decided on "possibly effective" in 1970. In response to this decision, Riker submitted four additional studies during 1971 and 1975. In 1975, the FDA evaluated the data, determined they were insufficient, and requested more. More data were submitted (primarily additional information for the 4th study) in 1975. In 1982, FDA again reviewed the data and determined they were insufficient, and finally in 1983, withdrew deanol from the market.

Based on the experience of physicians and researchers who have used deanol, it appears to be effective in some children. The characteristics of children who respond have not been defined, though they include both children who were and who were not responsive to methylphenidate. While this is very beneficial for the individuals who do respond (since there are little or no side effects) the "mean" effect on a group is diluted, resulting in a lack of statistical significance on many of the outcome variables in the clinical trials. This point has been well detailed by Oettinger (1977).

The data that had accumulated during the 1970's on the stimulant drugs surely affected the way that clinical trials were evaluated and contributed to the withdrawal of deanol from the market due to lack of compelling efficacy data for the indications. However, a review from 1967 shows a favorable comparison between deanol and medications used for "minimum brain dysfunction" including methylphenidate, amphetamines, chlordiazepoxide, chlorpromazine, reserpine, and miscellaneous tranquilizers and anticonvulsants (Millichap and Fowler, 1967). These authors reported that deanol was effective in 47% of children with only 7% reporting side effects.

The comparative study of deanol with methylphenidate and placebo is particularly strong regarding efficacy of minimal brain dysfunction and showed similar efficacy for both treatments (Lewis and Young, 1975). Seventy-four children referred for problems with learning, including many with hyperactivity, were screened for neurological or psychiatric illness, then given deanol, methylphenidate, or placebo in a double-blind fashion for 3 months. Maintenance dose for methylphenidate was 40 mg daily; for deanol, 500 mg. Behavior rating forms, reaction time, and a series of standard psychometric tests were given before and after treatment. Both products showed significant improvement on a number of tests; the pattern and degree of change differed slightly for the two. Deanol thus appeared to improve performance in children with learning and behavior disorders.

In addition, DMAE has been reported to have therapeutic effects on cognition as measured by EEG (Dimpfel et al., 1996). These are but some of the studies that support the beneficial effects of DMAE in children with ADHD-related symptoms, and additional studies have been reviewed by other experts in this case.

Phospholipid Supplementation

The phospholipids (PL) are the main foundational molecules for all cell membranes, serving much as building blocks for the membrane matrix into which the proteins are inserted. They include phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE),

phosphatidylinositol (PI). The phospholipids contain the EFAs such as the omega-3 and omega-6 polyunsaturated fatty acids (PUFAs). Of the phospholipids, PC is quantitatively the most common in all membranes and is the body's main reservoir for choline.

Neuronal (brain cell) membranes contain high concentrations of special lipids called long chain polyunsaturated fatty acids (LC-PUFAs), that are crucial components of the phospholipid bilayer. Neurotransmitter receptors lie embedded in the matrix of this membrane and their function is dependent on the phospholipids which give the unique shape and structure to the membrane. While brain cells do not appear to replicate themselves, their structural components, especially the phospholipids, are continually being degraded by oxidative stress and must be replaced. Thus, the supply of choline, dimethylethanolamine (DMAE), lecithin, and polyunsaturated fatty acids (omega-3 and omega-6) are essential for the generation of new phospholipids for optimal function of these membranes. Considerable evidence is now available that depletion of these lipids through dietary deficiency or through accelerated breakdown (due to oxidative stress), may result in a wide variety of behavioral disorders. Deanol and the phospholipids, such as those contained in Pedi-Active A.D.D., appears to work by supplying raw materials for the synthesis of phospholipids, and leading to increases in phospholipid production (Post et al., 1995) and incorporation.

Phosphatidylserine (PS) is clinically demonstrated to benefit a wide range of brain functions (Kidd, 1999). This phospholipid occurs in the brain at far higher concentrations than it does in the other organs. It is a key constituent of nerve cell synaptic membranes, which are involved in the production and release of neurotransmitters, and their action on receptors located on the membrane on the adjacent cell.

Ingested as a dietary supplement, phosphatidylserine (PS) appears to facilitate synaptic transmission. PS is widely used in Italy, Scandinavia, and other parts of Europe to treat various forms of age-related dementia as well as normal age-related memory loss. Phosphatidylserine is one of the many substances involved in the structure and maintenance of cell membranes, especially in the brain. Because the body manufactures phosphatidylserine, it is not considered an essential nutrient; however, a relative deficiency of phosphatidylserine may occur in certain types of health conditions and behavioral problems.

Many studies have evaluated the effects of supplemental phosphatidylserine in mice and rats, finding improvement in different measures of brain function. Treatment also appears to slow age-related changes in rat brain. Clinical studies on phosphatidylserine, conducted in the U.S. and abroad, have demonstrated positive results on brain function and memory.

Brain Structure and Phospholipids

LC-PUFAs are an essential component of nerve membrane phospholipids. These lipids are easily oxidized in the free state, but may be more stable when incorporated into phospholipids. Nevertheless, there appear to be individuals who have a relative deficiency of these fatty acids, due to either insufficient intake or metabolism and subsequent incorporation into membranes.

The necessity of these lipids for brain and behavioral development has received considerable attention over the last 50 years (Wainwright, 1992). Dietary fats clearly affect the levels of cholesterol, phospholipids, and sphingomyelin in brain microsomal and synaptosomal membranes (Foot et al., 1982). These changes in membrane composition resulting from the diet take place rapidly, and appear to be continuously modified according to lipids consumed (Innis and Clandinin, 1981).

Some children with ADHD (40% of a sample recently studied) show symptoms associated with fatty acid deficiency and have lower plasma phospholipid levels of 20:4n-6 (AA) and 22:6n-3 (DHA) – essential components of the structural lipids of neuronal membranes, particularly excitable membranes such as those at the synaptic terminal. These deficiencies may not be totally dependent on dietary intakes. There may be innate metabolic deficiencies that result in reduced ability to form and store these fats. Lower plasma levels of LC-PUFAs may reflect a relative deficiency of these fatty acids throughout the body. If deficiencies were found in the brain, the resulting membrane structural changes that would occur could well underlie the abnormal behaviors that children with ADHD show.

Mitchell et al., (1987) measured plasma fatty acids in 44 hyperactive children and 45 matched control subjects, and found the hyperactive children had significantly lower concentrations of DHA, AA, and the AA precursor DGLA (dihomo-gamma linolenic acid, C20:3 omega 6). Stevens et al., (1995) extended these results, and Stordy (2000) correlated the phospholipid deficiencies with symptoms of learning disabilities.

Stevens and her collaborators at Indiana University measured plasma and red cell fatty acid levels in 53 boys with ADHD and 43 controls, aged 6-12 years. They confirmed the lowered plasma concentrations of DHA and AA (but not of DGLA); and found plasma eicosapentaenoic acid (EPA, C20:5 omega 3) was decreased, as was red cell AA (Stevens et al., 1996).

Burgess et al. (2000) have reported that children having these lipid deficiencies had significantly more behavioral problems, temper tantrums, and learning, health, and sleep problems than did those children who did not. While the reasons for the lower proportions of LC-PUFAs in these children are not clear, factors involving fatty acid intake, conversion of EFAs to LC-PUFAs and to phospholipid products, and enhanced breakdown of these lipids appear to be central to the behavioral disturbances.

Despite the correlations of behavior problems with reduced levels of LC-PUFAs in humans and in animals, direct dietary supplementation with essential fatty acids alone has not been particularly successful in the general population. It is likely, however, that additional phospholipid components or the phospholipids themselves may be more beneficial than EFAs alone for children demonstrating difficulty with mental concentration, and other symptoms associated with ADHD.

In a study of 21 consecutive ADHD cases aged 4-19, dietary supplementation with PS benefited over 90 percent of the cases (Ryser, 2001). At intakes of 200-300 mg/day of PS for up to four months, attention and learning were most consistently improved.

DMAE and Phospholipids
Cells incubated with dimethylethanolamine incorporate more [3H]palmitic acid into the corresponding phospholipid, phosphatidyl-N,N-dimethylethanolamine (Jacobs et al., 1998). DMAE is also reported to have an antioxidant effect (Nagy and Floyd, 1984). Antioxidants have been shown to increase PUFA content in the phospholipid fractions of blood platelets (Pellegrini et al., 1996), probably by reducing its breakdown by oxygen radicals.

DMAE has been shown to enhance production of polyunsaturated phosphatidylcholines, increase fluidity and increase the proportion of polyunsaturated fatty acids within the membranes (Alvaro et al., 1989). These are critical physiological elements of normal neuronal function.

III. Conclusion

In sum, based on my review of scientific materials provided to me by counsel to Natural Organics, and other available data, it is my expert opinion that the advertising claims for the Pedi-Active A.D.D. dietary supplement are substantiated.

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Materials Sent to Dr. Jerry Cott

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. FTC, Dietary Supplements - An Advertising Guide for Industry
3. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Re of Riker Laboratories, Inc. Submission in Support Request for Hearing.
4. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)
5. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.
6. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application
7. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)
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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case, In the Matter of Natural Organics, Inc., and Gerald A. Kessler

William G. Crook, M.D.

I have been asked to provide an opinion regarding the scientific substantiation for advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I am a retired pediatrician, having practiced pediatrics, allergy and preventive medicine in my hometown of Jackson, Tennessee for over 45 years. In February of 1949, following completion of my medical education at the University of Virginia, Pennsylvania Hospital, Vanderbilt and Johns Hopkins, I opened my office to practice general pediatrics. I have served as Visiting Professor of Pediatrics at the University of California, San Francisco (1973), Ohio State University (1974) and the University of Saskatchewan (1976). I have written extensively on the subject of children's health, food sensitivities and allergies, and disorders generated by the prolonged and continued use of antibiotic drugs.

The FTC has alleged that Natural Organics' advertising includes the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;
2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

From my review of the clinical and other data relating to the ingredients in Pedi-Active, A.D.D., that is 2-dimethylaminoethanol bitartrate (DMAE) and phosphatidylserine-enriched lecithin (LECI-PS®), and based on my knowledge of this area, it is my opinion that the claims for Pedi-Active A.D.D. are substantiated by the scientific literature. A list of the information that I was provided for review is attached.

During the 1950's, I learned that systemic and nervous system symptoms in my patients were often caused by sensitivity to common dietary ingredients, as discussed in scientific articles published in the *Journal of Pediatrics* (1947) and *Pediatric Clinics of North America* (1953). In the mid-1950's, in the course of my medical practice, I found that "difficult" children, including children demonstrating behaviors associated with the condition now known as ADD/ADHD, such as inability to focus and to pay attention, could be helped by dietary changes. I also found that the use of different types of dietary supplements made a significant difference in many of my patients.

During my pediatric internship and residency at Vanderbilt University Hospital (1946-1948), I worked with Leon Oettinger, Jr., M.D., one of the Assistant Residents. During the late 1950s, 60s and 70s, we exchanged letters and he told me about his success in using deanol (2-dimethylaminoethanol) in his patients with behavioral disorders. Oettinger also sent me a copy of his article describing the use of deanol,

which was published in the *Journal of Pediatrics* (1958). As reported in the *Journal of Pediatrics*, Dr. Oettinger observed a decrease in overactivity, lengthening of the attention span, and a decrease in irritability, which, as Dr. Oettinger noted, would be expected to contribute to improved scholastic functioning.

Although I read his material with interest, my attention was focused on food sensitivities rather than medications of any type. During the 1970s (January 1, 1973 – December 31, 1978), I carried out a study using elimination/challenge diets in 182 of my patients with behavior and learning problems. I published my findings in the *Journal of Learning Disabilities* in 1980. A brief reference of this study was published in the *New England Journal of Medicine* in 1994: "The parents of 128 of these children reported that they were certain that their child's hyperactivity and other nervous system symptoms were related to one or more of the dietary ingredients."

It should be noted that, even in the most difficult children, the behaviors associated with the term "ADHD" have no common biological origin, but can be caused by a variety of stresses, including nutritional imbalances, environmental toxins and abusive environments. Not surprisingly, then, there is no uniform method of improving the symptoms of ADHD that will be effective for all children. This is true for approaches that include modification of the diet and dietary supplementation, as well as the use of drugs.

I've carefully reviewed several studies published in the peer reviewed literature concerning the use of a product called Deanol® (DMAE), formerly marketed by Riker Laboratories. I have also reviewed studies concerning DMAE conducted by C. Pfeiffer

and H. Murphree. I was impressed with their findings which showed that 25 of 35 students taking DMAE reported "greater daytime energy, attentiveness at lectures . . . better ability to concentrate on writing papers or studying."

In particular, the study by Lewis and Young (1975) found statistically significant positive results using deanol (DMAE), in a double-blind study that included a placebo control and an active methylphenidate group. The observers reported that the results with deanol (DMAE) demonstrated that, when given to children with minimal brain dysfunction, "can produce changes in a number of behavioral measures of approximately the same magnitude as seen with methylphenidate." Lewis and Young emphasized deanol's relative nontoxicity as an important point in its favor." Other studies conducted using deanol (DMAE) also produced positive results, as summarized by Dr. Osvaldo Ré, in his article, *2-dimethylaminoethanol (Deanol): A Brief Review of Its Clinical Efficacy and Postulated Mode of Action*, Cur. Ther. Res. (Nov. 1974), and demonstrated by C. Pfeiffer and H. Murphree. (*The stimulant effect of 2-dimethylaminoethanol (deanol) in human volunteer subjects.* Clinical Pharmacol. Ther. 1:303-310.)

Pedi-Active also contains phosphatidylserine (PS)-enriched lecithin (LECI-PS®), which includes other phospholipids. About 5 years ago, I became aware of important research studies conducted by Thomas H. Crook, III, Ph.D. (although we share the same name, we are not related). Dr. Crook has demonstrated that PS produces a positive effect in improving memory in older persons. (Crook, TH, Petrie, W. et al., *Effects of Phosphatidylserine in Alzheimer's Disease.* Psychopharmacology Bulletin,

28(1): 61-66, 1992; Crook, TH, Tinkelberg, J. et al. *Effects of phosphatidylserine in age-associated memory impairment.* Neurology 41(5):644-49, 1991). I have also reviewed the work of Dr. Parris Kidd regarding the use of PS and related phospholipids to supplement the diet of children who exhibit signs of inattentiveness and hyperactivity. (Kidd, P., *Attention Deficit/Hyperactivity Disorder (ADHD) in Children: Rationale for Its Integrative Management.* Alt. Med. Rev. vol. 5, no. 5:402-428, 2000.)

There is solid evidence in the scientific literature to support the use of DMAE, along with PS and other phospholipids, to improve symptoms in children who exhibit behavioral signs associated with ADHD, such as inability to pay attention, to focus and to learn. It is my opinion that Pedi-Active A.D.D. should be allowed to remain on the market with the advertising claims that the FTC has challenged in this case.

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Materials Sent to Dr. William Crook

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.

2. FTC, Dietary Supplements - An Advertising Guide for Industry

3. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Re of Riker Laboratories, Inc. Submission in Support Request for Hearing.

4. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)

5. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.

6. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application

7. NAS/NRC Deanol Panel Review

8. Lewis J, Young R. Deanol and methylphenidate in minimal brain dysfunction. *Clin Pharmacol Ther.* v. 17. n. 5. p. 534-40

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Leopold Galland, M.D.

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I am the Director of the Foundation for Integrated Medicine and have been in private practice since 1985. The focus of my practice and publications has been the utility of nutritional approaches for improving physical and mental health of adults and children with chronic illness. One focal point has been the effect of diet and nutritional supplementation in children with attention deficits, learning disorders and developmental delays.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D. For the purpose of this report, I have assumed that these are the claims made for the product.

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

Given my practice and my use of dimethylaminoethanol (DMAE) and phosphatidylserine (PS) in children in my practice for over a decade, I was familiar with much of the existing data on these ingredients in Pedi-Active A.D.D. prior to being contacted about this case. I also try to stay abreast of the literature pertaining to research that is relevant to nutritional approaches to ADHD. I have been provided with data and other information on DMAE and PS in the context of my review of the claims for Pedi-Active A.D.D., and a list of that information is attached. Much of the information that was provided related to data already familiar to me in the context of my research and practice.

In my practice, I deal with a broad spectrum of cognitive and behavioral problems, which are often divided into discreet entities (such as ADHD) for diagnostic purposes, even though there is a wide spectrum of behavioral problems for each diagnosis. Most individuals, however, do not fall neatly into any particular diagnosis, and individual patients often display overlapping symptoms that have some characteristics of several diagnoses. In short, the lines between many diagnoses are not clear, and while it is easier to define the ends of the spectrums of behavior for some diagnoses, such as autism, most patients do not display classic symptoms.

In addition to the array of behavioral problems that fit within any single diagnosis, with conditions such as ADHD it is generally recognized that there are a wide variety of

potential causes. Therefore, within any population of children diagnosed as ADHD, such as a population chosen for a clinical study, there will be a potential for both a spectrum of behavior and a spectrum of causes within that population. Further, it would be expected that, because of the variation, it is likely to be difficult to establish statistical significance in a clinical study, given that it is unlikely that children with an anomalous set of behavior and causes for that behavior will react in the same way to a test treatment. This is why it is important to look carefully at clinical data on the effects of nutrients on children with ADHD. Even relatively small but significant improvements may be very important because they may be indicative of very significant improvement in a subset of children that responded to the treatment.

My review of studies on DMAE in particular has led me to believe that DMAE, in the range of 200 to 400 mg per day, is a valuable tool for improving focus, attention and learning in children with ADHD. I have confirmed what these studies have shown in my practice. DMAE has repeatedly proven to be a dramatically effective treatment for improving attention, focus and learning in children who fall within the broad diagnosis of ADHD. In over ten years of practice parents have confirmed, in many cases in which DMAE has been used, that their children have responded with significant improvements in attention, focus and scholastic performance. Such improvements are documented in the office notes of my patient records.

I also use PS in children with ADHD as part of a nutritional support program for these children. Although the dose that I use, 100 to 300 mg per day depending on the age of the child, is higher than the daily dose used in Pedi-Active A.D.D., 60-80 mg per day,

the available data and my experience indicate that a lower dose would not be ineffective but would possibly take longer to show an effect. Therefore, the PS component of the product is also a basis for the claims made for the product even at a lower dose than I use in my practice. Given the combination of PS with DMAE in this product, I do not see this as a significant issue in terms of whether the claims for the product are substantiated.

Finally, I am aware of other physicians and nutritionists who use DMAE and/or PS in their practices to address learning and attention problems in children. I believe that this is a fairly common practice, and that this practice is the result of, and is based on, reliable data.

In conclusion, it is my opinion that the claims that the FTC has alleged have been made for Pedi-Active A.D.D. are substantiated by competent and reliable scientific data. Further, my own experience with children in my practice also shows that DMAE and PS help improve the symptoms commonly associated with ADHD, difficulty with attention, focus and learning.

Materials Sent to Dr. Leopold Galland

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.
3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)
4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.
5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application
6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)
7. FTC, Dietary Supplements - An Advertising Guide for Industry
8. Lewis J, Young R. Deanol and methylphenidate in minimal brain dysfunction. *Clin Pharmacol Ther.* v. 17. n. 5. p. 534-40
9. Re, O. 2-Dimethylaminoethanol (Deanol): A Brief Review of its Clinical Efficacy and Postulated Mechanism of Action. *Cur Ther Res*, v. 16, n. 11, Nov. 1974.
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12. Coleman N, et. al . Deanol in the Treatment of Hyperkinetic Children. *Psychosomatics.* vol. 17, April/May/June 1976. p. 68-72
13. Geller S. Comparison of a Tranquilizer and a Psychic Energizer- Used in Treatment of Children with Behavioral Disorder. *JAMA.* 174(5): 481-484. Oct. 1 1960
14. Kidd P. Attention Deficit/Hyperactivity Disorder(ADHD) in Children: Rational for Its Integrative Management. *Alt Med Rev.* 5(5): 402-428. 2000

Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Charles Gant, M.D., Ph.D.

I. Introduction

I have been asked to provide an opinion regarding the scientific substantiation for advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I am a medical doctor in private practice who has treated ADHD children for twenty years. In light of my experience as a doctor working holistically with ADHD children, I have been familiar with the ingredients in Pedi-Active A.D.D., (that is, a 2-dimethylaminoethanol and phosphatidylserine and related phospholipid compounds) for some time. I began using Pedi-Active A.D.D. in my practice in 1998.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D. For the purpose of this report, I have assumed that these are the claims made for the product. However, as a scientific expert witness, I do not offer an opinion as to the meaning of the advertisements.

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

Given my professional experience and knowledge of the available scientific data, including scientific studies provided to me by counsel to Natural Organics and the attached references, the data suggest and my clinical experience indicates that the advertising claims for Pedi-Active, A.D.D. are scientifically supported.

II. Analysis of Issues and Scientific Data

A. Background

Attention deficit / hyperactivity disorder (ADHD) is classified by the DSM IV (Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition) as a mental disorder primarily characterized by a "persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development." The clinician using the DSM-IV should, however, consider that individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis. Furthermore, "boundary cases" will be difficult to diagnose.

Thus, while individuals with ADHD may present with similar behavioral manifestations, their underlying makeup is likely to be heterogeneous. A significant body of peer-reviewed scientific literature strongly supports that conclusion, authored by the Task Force on DSM-1V: individuals with ADHD are indeed a heterogeneous group, with each individual likely to have a unique array of presumably etiological biochemical conditions that *in toto* for each individual are expressed symptomatically as ADHD. Such factors would include: genetics, diet/nutrition, lifestyle, stressors, and toxins.

Many studies have suggested that ADHD is correlated with a multiplicity of physiological factors. These studies cluster around eight general areas, including food and food additive allergies, heavy metal and other xenobiotic toxicities, B vitamin and phytonutrient deficiencies, amino acid and metabolic deficiencies, thyroid-related conditions, low protein/high carbohydrate diets and/or insufficient glucose/protein metabolism, essential fatty acid (EFA) and phospholipid deficiencies and deficiencies in essential mineral levels.

In the course of my medical practice, I have personally interpreted extensive physiological laboratory testing on hundreds of children with behavioral symptoms associated with ADHD in order to determine the unique physiological risk factors in each individual and target a specific intervention. The conclusions that can be gleaned from this clinical work and research include:

1) The heterogeneity of ADHD individuals is so great that the likelihood that any two children would have exactly the same physiological profile is infinitesimal.

2) Reversal of only one or two physiological "abnormalities" in ADHD individuals who have many such imbalances, is often sufficient to correct the ADHD behavioral manifestations.

3) Each physiological variable coexisting within each individual with ADHD does not exert its effect independent of the others, but in fact each plays synergistic roles to counteract other physiological imbalances and/or deficiencies.

4) Nutritional interventions for ADHD that are done by parents (which might be the case, generally) without professional guidance often produce positive results, but professional guidance would be expected to improve efficacy. In other words, professional assistance is often not necessary for each individual with ADHD. In any event, considering the excellent safety profile of Pedi-Active A.D.D., there would not be an "downside" to parents using the dietary supplement.

B. Analysis of the Scientific Evidence Supporting Claims for Pedi-Active A.D.D.

Pedi-Active ADD is a dietary supplement containing the dietary ingredients, DMAE (2-dimethylaminoethanol) (also known as N,N' dimethylethanolamine) and phosphatidylserine-enriched lecithin (LECI-P5®). DMAE has been found in and extracted from, among other sources, salmon roe (260 µgm./kgm. unbound and 1662 µgm./kgm. bound), pig brain (173 µgm./kgm. unbound and 73.5 µgm./kgm. bound) and human brain (5.1 µgm./kgm. unbound and 76.4 µgm./kgm. bound). Phosphatidylserine is a naturally occurring phospholipid commonly derived from soy.

Scientific studies demonstrate that DMAE has a beneficial effect on individuals with ADHD. Given the panorama of biochemical and environmental interactions (e.g., toxic metal and other toxicities, vitamin and mineral deficiencies, food allergies, etc.) found to be associated with ADHD, for DMAE to be effective, its mechanism of action would have to be pervasive in order to override the effects of so many potential causalities. DMAE is best known for its role as a precursor for choline and phosphatidylcholine (PC). Since phospholipids do indeed play so many important physiological roles, the phospholipid enhancing potential of DMAE, as a methyl donor for PC biosynthesis, is the putative mechanism for DMAE's ability to override some of the risk factor categories discussed above.

Choline is converted to phosphatidylcholine in a series of reactions involving ATP, cytidine triphosphate (CTP) (a nucleotide derivative) and diacyl glycerol (DAG). Phosphatidylcholine can be converted into phosphatidylserine, provided that a sufficient supply of serine is available, which is converted back to choline as part of the exchange. Phosphatidylserine in turn can be converted into phosphatidyl ethanolamine which, in turn, in three successive methylation steps requiring S-adenosylmethionine can be converted back into phosphatidylcholine. Thus the phospholipids are interconverted to meet the requirements of cell membrane construction and repair. Phosphatidylcholine and sphingomyelin (constructed from choline and serine) preferentially align themselves in the outer leaflet of the cell membrane and phosphatidyl ethanolamine and phosphatidylserine are found on the inner leaflet. The enzyme "flippase" ensures that this inner/outer preference between different phospholipids is ensured.

Thus, supplementation with either a choline precursor (DMAE) or phosphatidylserine, as occurs with the product PEDI-ACTIVE A.D.D., will potentially drive a cascade of phospholipid interconversions to fortify cell membranes or promote any of the twelve functions of phospholipids listed above. Combining them into one preparation as is done with the dietary supplement product PEDI-ACTIVE A.D.D., would be expected to result in the nutritional

enhancement of each ingredient. As regards the issue of phospholipid function, either a higher dosage of DMAE or phosphatidylserine alone should accomplish the same objective as a proportionately lower dosed combination product.

DMAE's role in ADHD is based on its neurotransmitter methyl donor and precursor effects, in addition to its more general phospholipid enhancing role. A mechanism of catecholaminergic stimulation or a modulatory cholinergic inhibition is being sought. The rationale for this is based on the fact that the therapeutic mechanism of psychostimulant medication is generally thought to be derived from its dopaminergic agonist effects, and a great deal of evidence suggests that an oppositional relationship between the catecholaminergic and cholinergic systems exists.

DMAE appears to act as a methyl group donor to 'spare' the metabolic pools of active methyl groups available for the synthesis of PC, and other methyl containing nutritional biochemicals in the brain. If choline levels were very low, DMAE would be expected to fill a precursor role for both the synthesis of acetylcholine and phosphatidylcholine (and eventually phosphatidylserine and other phospholipids). If choline levels were adequate or high, DMAE could inhibit the formation of both acetylcholine and phosphatidylcholine by competing for brain uptake.

In a double blind, placebo controlled study, DMAE in combination with a vitamin and mineral supplement showed a statistically significant EEG improvement in the fronto-temporal cortex during both the memory and symbol recognition tests. The fronto-temporal cortex is a region known to be dopaminergically innervated.

Many studies demonstrate that phosphatidylserine (PS) supplementation produces beneficial effects on heterogeneous neurochemical processes and the behavioral manifestations thereof. In a physician in-office study of 21 consecutive ADHD patients between the ages of 4 to 19, phosphatidylserine supplementation achieved a greater than 90% efficacy. Considering the multiplicity of roles played by phospholipids in membrane-receptor functions and the ordering of cellular metabolic processes, an exact rationale for their efficacy in affecting conditions involving a multiplicity of factors, such as in children characterized as ADHD, is difficult to precisely define at this time. Nonetheless, it is well established in the scientific literature that the functions of phospholipids include the following:

1) They are high-energy, basic, structural, and functional elements of all biological membranes, such as cell, blood corpuscles, lipoproteins, and surfactant.

2) They are indispensable for cellular differentiation, proliferation and regeneration.

3) They maintain and promote the biological activity of many membrane-bound proteins and receptors.

4) They play a decisive role for the activity and activation of numerous membrane-located enzymes, such as sodium-potassium-ATPase, adenylate cyclase, and lipoprotein lipase.

5) They are important for the transport of molecules through membranes.

6) They control membrane-dependent metabolic processes between the intracellular and intercellular space.

7) The polyunsaturated fatty acids contained in them, such as linoleic acid, are precursors of the cytoprotective prostaglandins and other eicosenoids.

8) As phosphatidylcholine (PC), the predominant fatty acid donor, they have an influence in certain neurological processes.

9) They emulsify fat in the gastrointestinal tract.

10) They are important emulsifiers in the bile.

11) They codetermine erythrocyte and platelet aggregation.

12) They influence immunological reactions at the cellular level.

Two of the most important phospholipids (especially in the nervous system), phosphatidylserine (PS) and phosphatidylcholine (PC), interdigitate their fatty acid chains to form the phospholipid-protein bilayer of cell membranes. Obviously, having sufficient amounts of serine and choline to serve as the structural backbone holding the fatty acids in place, is critical. Having tested hundreds of children with symptoms associated with ADHD for serine deficiency, as well as RBC membrane essential fatty acids, I have concluded that deficiencies in all of these membrane precursor agents are very common in this heterogeneous population.

III. Conclusion

In short, Pedi-Active ADD could be a part of or the only treatment for a complementary/alternative protocol for ADHD. Based on my knowledge of the available scientific data, including a review of information provided to me by Natural Organics' counsel, as well as my experience as a clinician using the Pedi-Active A.D.D. dietary supplement, it is my opinion that the advertising claims for the product are scientifically supported.

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Dr. Edward M. Hallowell
The Hallowell Center for Cognitive and Emotional Health

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. The FTC has alleged that Natural Organics's advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

I have reviewed information and studies that have been provided to me that are relevant to the claims above (see attached list). As a basis for forming an opinion as to whether the claims alleged by the FTC are substantiated (assuming that the FTC is

correct in its allegations), I have also relied on my experience in private practice and teaching, and my knowledge of the role that both therapeutic drugs, nutrition, and other methods of addressing ADHD.

ADHD is a diagnosis that covers a wide spectrum of behavioral problems, including the attention and learning difficulties that are the subject of the advertising claims for Pedi-Active A.D.D. ADHD also has a wide range of potential causes, including emotional stresses, nutritional issues, and other environmental and physiological factors. As a result, the diagnosis and treatment of ADHD is complex. No single approach is accepted in the scientific and medical community as the best approach. Often, a combination of methods yields the best results, and there is a high degree of individual variation in the reaction of children to any one treatment method.

The published literature I have reviewed shows that, in some cases, the ingredients in Pedi-Active A.D.D. improve the ability of children with the symptoms of ADHD to focus and therefore learn better. In short, it is my opinion that there is substantiation for the claims that the FTC alleges have been made for Pedi-Active A.D.D.

Materials Sent to Dr. Edward Hallowell

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.

2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case

In the Matter of Natural Organics, Inc. and Gerald A. Kessler

Parris M. Kidd, Ph.D.
Nutritional Consultant and Biomedical Educator

I. Introduction

I have been asked to provide an opinion regarding the scientific substantiation for advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I earned my Ph.D. degree from the University of California at Berkeley in zoology and cell biology, and did post-doctoral training and NIH-sponsored independent research at the University of California San Francisco Medical Center in cardiovascular anatomy and pathology. I have extensive research and teaching experience in both the basic and clinical life sciences, and have been active in the nutritional field since 1983. I am an experienced consultant to the dietary supplement industry, and an independent biomedical educator.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

As a scientific expert, I cannot offer any opinion as to what the advertisements mean as a matter of FTC law, or whether Natural Organics's advertisements actually make these claims, as the FTC has alleged.

Assuming for the sake of argument that the FTC is correct in its assertion that Natural Organics's advertisements include claims that the dietary supplement Pedi-Active A.D.D. will improve the attention span and scholastic performance of children who have ADHD or who have difficulty focusing on school work, and will treat or mitigate ADHD or its symptoms, it is my opinion that these claims are adequately substantiated by scientific data. It is also my opinion that the product does not raise any safety issues.

II. Analysis of Issues, Scientific Studies and Data

I intend to make myself available to testify to the suitability of supplementing children's daily dietary intakes with (a) dimethylaminoethanol (DMAE), bitartrate salt, (b) a lecithin preparation containing phospholipids (PL) as the main active constituents and enriched in phosphatidylserine (PS), in order to support or enhance certain of brain functions, such as attention, behavioral control and learning. I have had clinical exposure to such children, having participated in two studies that explored the benefits of PS against such problems. I normally maintain in-depth files on these topics and on both the nutritional constituents in question, and for this project I did updates through searching online databases and other primary reference sources. I also received additional scientific material by way of Natural Organics' counsel, a list of which is attached.

I intend to focus my expert contributions on the scientific evidence for the following assertions:

1. That DMAE is a nutrient that has pro-homeostatic (life-supporting) actions which augment those of choline, an essential nutrient important for human brain development and neurological function;

2. That choline is linked to biochemical processes in the brain that specifically support learning, attentional and behavioral control;

3. That DMAE provides clinically significant benefits to some children who have difficulties with maintaining attention and/or behavioral control and/or learning;

4. That phosphatidylserine (PS) and the other phospholipids (PL) present in Pedi-Active A.D.D. are pro-homeostatic nutrients essential to normal, healthy brain functions;

5. That some proportion of children with learning, attentional and behavioral control problems are likely to derive clinically significant benefit from PS-PL; and

6. That a clear scientific rationale exists for mutual, pro-homeostatic enhancement of children's brain functions by DMAE and PS-PL.

The product in question, Pedi-Active A.D.D., consists of two major active dietary ingredients, namely:

1. Dimethylaminoethanol, commonly called DMAE, as its bitartrate salt.

2. A lecithin concentrate containing various phospholipids and enriched in phosphatidylserine (PS).

1. DMAE (2-dimethylaminoethanol) is a nutrient that occurs naturally in the lower life forms, in animals, and in the human body. DMAE is closely chemically related to choline, and can be utilized by the human as a partial substitute for choline. Choline is a precursor substance for the major chemical transmitter acetylcholine (ACh), which is centrally involved in the brain processes that underlie learning and memory formation and the maintenance of attention.

When taken by mouth DMAE is readily bioavailable, and it crosses the blood-brain barrier to reach the brain, with more facility than does choline. DMAE can be utilized by choline acetylase, the enzyme which catalyzes ACh synthesis.

DMAE has other proven roles in human biochemistry which further support its utility as a dietary supplement for brain support. As one instance, DMAE can become incorporated into phospholipids, which are biochemical building blocks for the cell membrane systems of neurons. These membranes are the sites on which the majority of the brain's functions are grounded. The acetylcholine chemical transmitter system, which largely mediates attentional and learning processes, depends heavily on optimal functioning of the nerve cells' membrane systems.

Oxygen free radical production is obligatory to all things that live in the presence of oxygen, and cumulative "wear and tear" from intrinsically produced oxyradicals may be the eventual limit to the length of life. DMAE is an effective scavenger of the hydroxyl free radical which, of all the known oxygen-centered free radical species, is thought to be the most reactive and potentially the most damaging to the biomolecules located within and around the nerve cells of the brain. Since the metabolic load of hydroxyl free radicals provides an ongoing challenge to the brain's performance, this free radical scavenging capacity of DMAE lends an impressive additional dimension to its capacities to nutritionally support brain structure and function.

A number of controlled clinical trials and other clinical studies on DMAE with children are published in the peer-reviewed scientific literature. Their premises, designs, and numbers of subjects vary. Viewed as a body of data, the findings from these studies clearly indicate that some children benefited from DMAE by manifesting attentional, learning and behavioral improvements that were superior over children not so treated.

2. Lecithin is a food substance that is generally regarded as safe (GRAS). The active constituents of lecithin are overwhelmingly phospholipids. These are a group of nutrients with

diverse importance for homeostasis and for the overall support of human health. Phospholipids are present in all forms of life, from the most primitive single celled organisms to all cells of the human organism. Phospholipids are ubiquitous in the food supply, and their safety for human intake is firmly established.

The particular lecithin preparation used in Pedi-Active A.D.D., branded LECI-PS®, is further enriched in one phospholipid constituent, namely phosphatidylserine (PS). Like the other phospholipids of lecithin, PS is present in every single living organism. However, PS is concentrated in the human brain at far higher levels occur than elsewhere in living systems.

PS has been thoroughly researched for its biochemistry, metabolism, and functional involvement in the nerve cell networks of the brain. Some 18 double-blind trials have been conducted with PS, far more than are generally conducted with pharmaceuticals to meet FDA approval. Hundreds of peer-reviewed research publications document the involvement of PS in virtually every measurable aspect of human brain function.

Phosphatidylserine is an irreplaceable biochemical constituent of the brain. The presence of PS in the membrane systems of the nerve cells makes possible the generation and transmission of electrical impulses. The nerve cells' membranes are the initiation points for electrical currents that pass along the individual cells, then are relayed from cell to cell by way of contact structures called synapses. PS specifically facilitates the functioning of ion transport proteins that are located within these membranes.

Phosphatidylserine is also required for the packaging and release of electrically active natural substances, the *chemical transmitters,* that make possible the coordination of nerve cell activity into organized networks or *circuits*. Among the chemical transmitter systems facilitated by PS are those for acetylcholine and dopamine, both of which are centrally involved in learning processes, recording new memories, and attentional processes.

Phosphatidylserine is a specific constituent of the nerve cell membranes that carry protein kinase C, a bioenzyme complex which, in experimental animals, has been directly linked to learning mechanisms. Taken altogether, the diverse proven mechanisms by which PS contributes to human brain function render it scientifically and clinically worthwhile to investigate whether PS would benefit pediatric brain dysfunctions.

In early 1997, together with Richard Kunin, MD, a physician in private practice in San Francisco, I initiated a pilot study of PS in five children with attentional and/or behavioral and/or learning difficulties. After signing an Informed Consent form, the parents allowed their children to be evaluated by Dr. Kunin, with myself in the office as an observer. They also filled out a behavioral checklist on their child, and a global rating of their child's condition as compared with other children in his/her age range. Dr. Kunin did a clinically validated attention span test (finger-tapping) and other skills assessments, and took a detailed developmental and behavioral medical history. The parents were given phosphatidylserine capsules to take home. As part of the study design no other dietary supplements or medications were given, and a diet record was taken but no dietary changes were recommended.

Of the four children who complied, i.e., took the phosphatidylserine capsules daily during the treatment and observation period, three were significantly improved at the end of 6 weeks. One, a four and a half year old boy, began the study with poor behavior at school, inability to focus his attention, impulsivity, impatience, and frequent tantrums. After being on PS for 6 weeks, marked improvement was evident: his attention span and task performance improved, as did his patience and impulsivity, anxiety, overexcitement, destructive behavior, and ability to get along with other children. Very unlike his first visit, in the doctor's office he was able to sit quietly and play while the adults were talking. His mother said: "this is the first time he has ever been able to play normally." Dr. Kunin noted: "I have never seen a child this bad-off come around this much or this quickly."

Another case in this study was a six year three months old boy, pleasant and cooperative but very distractible and complaining of poor memory. At school he got confused, sat in the wrong place, talked too much and screamed when frustrated. After PS, his behavioral checklist score was substantially improved. His most intense symptoms – restlessness and impulsive behavior – both improved; he was better able to focus attention and follow rules at school and also had improved at home. His anxiety and depression were improved, and he performed better in his tests at school and in his attitude towards the classroom.

In 1998 I was approached by another medical physician, Carol Ann Ryser, M.D., to assist her with investigating whether PS would benefit children entering her practice with attentional and behavioral problems severe enough to negatively impact their social and academic performance.

Dr. Ryser's strategy for medical management involves providing such children with all the diagnostic, pharmacological, nutritional, and behavioral modification options necessary for quality care. She places each ADHD child on an individualized regimen which combines nutrients, drugs as indicated (including Ration where judged necessary), treatment for gastrointestinal imbalances, counseling, and other interventions. With the informed consent of the parents, 28 children in sequence were first oriented to Dr. Ryser's usual individualized regimen, then were provided PS without charge as an addition to their regimen. Over a period of more than two years, these children were followed through periodic visits and appropriate objective assessments.

Some 28 children aged 3-19 completed the study. Twenty-four (24) of the 28 patients (86%), benefited from PS over and above the benefits of medication. Two others (7%) experienced partial benefit from PS, while in another two (7%) benefit was unsure. Among the children who benefited, PS had a consistently calming influence on disruptive behavior patterns. It improved attention, concentration, and memory retention, and benefited academic

performance. Many of the children entered the study with depression and anxiety, and taking PS consistently benefited their mood.

The two aforementioned clinical studies with PS on "problem children" were not controlled studies and cannot be ranked as more than exploratory. Still, the benefits to quality of life for the children's parents, other family members, and last but not least the child himself, were evident and inestimable in value. No adverse effects or drug interactions were recorded with PS in this pediatric population. The excellent tolerability of PS to children is consistent with its 20-year record of clinical use and with its ubiquity as an *orthomolecule* in life forms from humans to single-cell organisms.

The optimal daily intakes of DMAE and PS-PL necessary to achieve positive results in children with respect to focus and learning has not been precisely determined at present, and may indeed vary somewhat on a case-by-case basis. Both DMAE and PS are nutrients that, when consumed as dietary supplements, will build up slowly over a period of weeks, which should come as no surprise since both are pro-homeostatic rather than pharmacologic. In the case of Pedi-Active A.D.D., daily intakes resulting from use of the product three to four times a day as recommended, would be expected to produce the most readily discernible results.

In addition to the materials already discussed, my opinion will also be based, in part, on the reports and testimony of other expert witnesses involved in this case, as well as my general scientific knowledge in this field.

III. Conclusion

I hold the firm opinion in this case, that both DMAE (dimethylaminoethanol), and PS (phosphatidylserine) with its associated phospholipids, are safe nutrient preparations with excellent rationales for efficacy in children with developmental or acquired problems in attention, behavior, or learning. From the outset of clinical research with DMAE several decades

ago, experts have disagreed as to its true degree of benefit for children with attentional, behavioral or learning problems. But honest experts often do not come to total agreement on any issue related to human health. Viewed as a whole body of data, the available findings indicate that most of this pediatric population will benefit to some degree from DMAE. The clinical research with PS on children is still in its infancy, but the exploratory findings indicate it makes a positive difference to the majority of children studied (total 33 in all).

After taking into consideration that (a) orally ingested DMAE reaches the brain; (b) DMAE becomes incorporated into phospholipids; (c) PS and other phospholipids are indispensable "building blocks" for the membranes of nerve cells; and (d) the vast majority of the brain's metabolic functions occur on such membranes; I conclude that pro-homeostatic, reciprocal enhancement of brain functions by these ingredients in Pedi-Active A.D.D. is a reasonable scientific certainty. To date, this is borne out by clinical verification of benefit from both of these nutrients.

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Materials Sent to Dr. Parris Kidd

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.

2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.

3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)

4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.

5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application

6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)

7. FTC, Dietary Supplements - An Advertising Guide for Industry

8. Geller S. Comparison of a Tranquilizer and a Psychic Energizer- Used in Treatment of Children with Behavioral Disorder. *JAMA*. 174(5): 481-484. Oct. 1 1960

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Richard A. Kunin, M.D.

Introduction:

I have been asked to provide an opinion regarding advertising claims made for the PediActive A.D.D. dietary supplement product that is at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler.

Qualifications:

I am a board-certified psychiatrist (1962) and recipient of an NIH special fellowship in neurophysiology in the department of neurology at Stanford Medical Center (1962-1963). My professional activities have focused on behavior therapy and nutritional biochemistry for the past 35 years, including published clinical research. In 1988 I presented my observations on over a hundred patients treated with dimethylethanolamine (DMAE) at the Princeton (NJ) Brain-Bio Center, a conference organized by Dr. Carl Pfeiffer, himself an early investigator into clinical applications of this nutrient-derived substance. In 1998, I participated in a small pilot study of the effects of phosphatidylserine, a parent substance of DMAE, in ADHD. I have been a consultant to the Autism Research Institute since 1995 and on the board of directors since year 2000.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D., and I have assumed for the purpose of this report that these are the claims that have been made for the product:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD (Attention Deficit/Hyperactivity Disorder).

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

The claims for Pedi-Active A.D.D. are supported by competent and reliable scientific data. I have reviewed information and studies that relate to the product, Pedi-Active A.D.D. and a list of that information is attached. I have also relied on my general professional experience and knowledge of research in the area psychiatry, ADHD, DMAE and nutrients.

Opinion:

It is my opinion that the claims for Pedi-Active A.D.D. are substantiated both by the scientific literature, which provides a reasonable basis for the effect that the constituents of the product have on the brain, and by the clinical data that show that some children in double-blind placebo-controlled studies have benefited from DMAE at doses comparable to those contained in Pedi-Active A.D.D.

I am aware that DMAE has not been shown to cause improvement in all children with attention, focus and learning problems commonly associate with ADHD. However, this is to be expected with a condition such as ADHD that is still debated in scientific circles. Competent and reliable scientific data show that

products like Pedi-Active A.D.D. will work in some children, but not in others. This is exactly what I and others who use DMAE in their practices have observed.

Because of the lack of safety issues and the physiological manner in which nutritional approaches to conditions like ADHD work, the standard for substantiation that should be applied to nutritional products like Pedi-Active A.D.D. is not the same standard that is applied to drugs with known adverse effects. The quantity of data that exists in support of the benefits that Pedi-Active A.D.D. on attention, focus and learning in some children diagnosed with ADHD surpasses what should be required for the marketing of nutritional products.

I view Pedi-Active A.D.D. as a valuable contribution to the range of nutritional products that could be of benefit to children with ADHD. Eliminating any claims that would guide parents of children with ADHD to try this product, would be unacceptable in light of the data supporting these claims.

Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case

In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Lester Packer, Ph.D.
Adjunct Professor
Department of Molecular Pharmacology and Toxicology
University of Southern California

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. Presently, I am an adjunct professor in the Department of Molecular Pharmacology and Toxicology at the University of Southern California. From July 1961 until June 30, 2000, I was Professor of Physiology in the Department of Molecular and Cell Biology at the University of California at Berkeley and a Senior Scientist at the Lawrence Berkeley National Laboratory. I have generally focused my research on nutritional biochemistry and the role of biological antioxidants in human health.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

I have assumed for the purpose of this report that these are the claims that have been made for the Pedi-Active A.D.D. dietary supplement product. As a scientific expert, however, I do not offer an opinion as to the meaning of the advertisements.

While I am not an expert in ADHD, I am an expert in the field of nutritional biochemistry and the physiological effects of dietary ingredients on human health. I have reviewed scientific materials concerning the ingredients in Pedi-Active A.D.D., that is, 2-dimethylaminoethanol (DMAE) and phosphatidylserine, including related phospholipids found in LECI-PS®, provided to me by Natural Organics' counsel. In providing an expert opinion in this proceeding, I am also relying upon my general knowledge of nutritional biochemistry and the effects of dietary substances upon bodily structure and function.

A biochemical, physiological basis exists to support the use of 2-dimethylaminoethanol (DMAE) and the phospholipids found in the Pedi-Active A.D.D. dietary supplement product. The rationale relies on results of studies conducted in animals, as biochemical investigations in the brain of human subjects are precluded. In addition to the opinion set forth below concerning the effects of these ingredients on neurological function, it is also my expert opinion that the product does not raise any safety issues.

Scientific studies demonstrate that DMAE, when consumed orally, enhances choline levels in the brain. Vincent Du Vigneaud et al (The Role of Dimethyl-and Monomethylaminoethanol in Transmethylation Reactions in Vivo, *J Biol Chem* 1946) showed, using a synthesized deuterated DMAE (a non radioactive heavy atom labeled form with deuterium isotope labeled methyl groups), that DMAE can be introduced into the diet and analyzed in substances with great accuracy by mass spectrometry. By feeding laboratory animals a diet deficient in choline and methionine, these investigators found that deuterated methyl groups subsequently appeared in choline isolated from tissues, demonstrating that the methyl groups of DMAE are used by the rat in the synthesis of choline.

That DMAE would assume, as the investigators noted, a pivotal position as both the immediate precursor and the principal demethylation product of choline, is important to brain functions, according to the rationale described below. Choline is a vitamin substance (hydroxyethyl trimethyl ammonium compound) that is a component of phosphatidylcholine (PC), an essential component of all biological membranes (in every cell and tissue of the body) and also in acetylcholine (AC), the neurotransmitter substance which is synthesized from acetate and choline by the enzyme choline acetylase (also called choline acetyl transferase). Acetylcholine is present in many tissues in the body, including the brain, and is responsible for synaptic transmission of nerve impulses, especially in muscle and nervous system tissues. Acetylcholine is released at the neuromuscular junction initiating contractility, i.e., a cholinergic nerve transmitter substance. Acetylcholine is necessary for vital brain functions, including learning and memory. An imbalance in brain acetylcholine may be a factor in children who have difficulty with attention, focus and concentration. Restoration of homeostatic concentrations of acetylcholine would be expected to improve the ability to concentrate and to focus.

Other studies have also reported enhanced choline levels by dietary intake or administered DMAE using radioactive DMAE administration (Dormand, Levron & Le Fur 1975). In vivo metabolism of the "false cholinergic precursor," a DMAE derivative, has been reported (J. Pharmacol Ther 185 235:157-61). These studies indicate that the methyl groups from DMAE reach the brain.

Methyl donors which contribute to choline biosynthesis are very important to brain function. This is because it is generally thought that choline in phosphatidylcholine (PC) and acetylcholine itself are derived only from the diet and that choline is not synthesized in the body.

Phospholipids, essential structural components of the brain, are vital for the proper functioning of brain neurotransmitters. Indeed, membrane integrity, fluidity, lipid-protein interactions, including membrane enzymes and receptor activation by ligands (e.g., hormones, cytokines, etc.), which trigger signal transduction and gene expression in the brain absolutely depend upon membrane structural integrity conferred by phospholipids and other lipid components such as cholesterol and sphingomyelein.

PC is needed in the diet to promote the intestinal absorption of cholesterol, another lipid component absolutely essential for biological membranes to regulate membrane fluidity and functionality, which, as explained above, is important for the fluidity of brain membranes. Recent studies suggest that PC in the gut is hydrolyzed to its triglyceride component, but the exact mechanism of internalization is not known. However, studies in the scientific literature indicate that phospholipids, such as PS, have beneficial effects in age-related memory impairment. (Crook et al Neurology 41;644,1991). Such studies attest to the bioavailability of oral phosholipids.

Other studies have demonstrated that DMAE is a potent hydroxyl free radical scavenger. Any molecule with one or more unpaired electrons is a free radical. Free radicals are highly reactive molecules that can be toxic in the body. The hydroxyl radical is among the most reactive in causing extensive molecular damage. It is formed during metabolism itself, and produced by environmental sources and stressors, such as environmental toxins. Electron paramagnetic resonance studies demonstrate the ability of DMAE to prevent and inhibit these most dangerous of radicals in biological systems from accumulating. (Zs.-Nagy & Floyd Arch Gerontol Geriat 3;297-310,1984). Another study addressing the effect of DMAE on suppressing the release of free radicals was shown using leukocytes obtained from animals and human subjects (Dolganiuc et al Arch Microbiol Immunol 57;23-32,1998). Quenching of free radicals produced by activated immune system cells will prevent injury to nearby normal healthy tissues. Indeed, it has been extensively documented that free radicals are toxic to brain tissue and that neuroprotective substances include those with radical scavenging properties. I have edited two books on this subject. (See Poli, Packer et. al, Free Radicals in Brain Pathophysiology, Marcel Dekker Inc., 2000; Packer, Hiramatsu et. al, Free Radicals in Brain Physiology and Disorders, Academic Press Inc. 1996).

In sum, it is my expert opinion that DMAE and the phospholipids present in the Pedi-Active, A.D.D. dietary supplement will support brain receptor functions, including cholinergic transmission and the integrity of neuronal and myelin membranes, which would be expected to support improved mental function, with concomitant improvement in the ability to concentrate and focus.

Materials Sent to Dr. Lester Packer

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.
3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)
4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.
5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application
6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)
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20. Pfeiffer CC, Jenney EH, Gallagher W, et al. Stimulant effect of 2-dimethylaminoethanol- possible precursor of brain acetylcholine. *Science* 126: 610-611. 1957

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45. Goldberg, A. Is Deanol a Precursor to Acetylcholine? *Dis Nerv Sys* Dec. 1977. p. 16-20

46. Coleman N, et. al . Deanol in the Treatment of Hyperkinetic Children. *Psychosomatics*. vol. 17, April/May/June 1976. p. 68-72

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Dr. Osvaldo Re

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D. For the purpose of this report, I have assumed that these are the claims made for the product.

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

When in private practice, I used dimethylaminoethanol (DMAE) in children to address focus, attention and learning problems commonly associated today with ADHD. I also worked for Riker Laboratories from 1966 to 1983 during a time when their deanol (DMAE) product marketed under the trade name Deaner was undergoing FDA review for efficacy. I was therefore familiar with much of the data available for DMAE prior to being contacted regarding this case. I have been provided with data and other information on DMAE in the context of my review of the claims for Pedi-Active A.D.D. A list of the information that I have been provided is attached, as well as a list of additional references of which I am aware and have relied on for my opinion. Some of the articles from this reference list are also attached.

Introduction

What today we call ADHD (Attention Deficit Hyperactivity Disorder) or simply ADD was formally known as MBDS (Minimal Brain Dysfunction Syndrome) and earlier was variously described as Childhood Hyperkinesis, with or without Behavior and Learning Problems. We have settled on "Attention Deficit Disorder." ADD or ADHD seem to now be the accepted terms to describe such disturbances affecting these children. It is estimated that the syndrome occurs in 5 to 10% of school-age children and its incidence is greater in boys than girls.

The cluster of ADHD symptoms is complex and somewhat confusing to the point that some experts believe that these do not amount to a disease entity. However, whatever the perception about ADHD, the fact remains that some children, while at school or home, do exhibit to varying degrees restlessness, overt hyperactivity, distractibility, inattentiveness, impulsiveness, emotional lability, inability to focus, short attention span and associated learning difficulties. These symptoms can be grouped as a syndrome, distinguishable from defined illnesses such as mental retardation, sensory deficiencies and epilepsy.

The management of children with ADHD requires a comprehensive approach directed at the conditions at home and school. It involves attention to the social environment of the child, to academic needs and shortcomings, consideration of nutritional factors and possible dietary changes, and appropriate educational resources. Psycho-social integration of efforts should include parents, teachers and health care professionals.

Deanol : 2-(Dimethylaminoethanol) or DMAE was marketed as its acetamidobenzoate salt by Riker Laboratories, Inc. under the trade name of Deaner.® Its main clinical application was as a component within a comprehensive approach to the treatment of children with Hyperkinetic Behavior and Learning Difficulties.

It has been postulated that the underlying mechanism of action of DMAE is that of facilitating the expression of central cholinergic activity. Therefore, earlier research work was directed to demonstrate that DMAE was a precursor of brain acetylcholine. Du Vigneaud in 1946(2) and Artom and Crowder in 1949 (3) had already demonstrated that DMAE was a precursor of choline in the hepatic tissue of rats.

Pfeiffer in 1957(4) postulated that DMAE was a precursor of brain acetylcholine. In 1958, Groth (5) working with 14C labeled Deanol demonstrated that, in mice, DMAE crosses the brain blood-brain barrier and is incorporated and retained in the brain.

In 1966, Mahler and Cordes (6) showed that DMAE is metabolized by phosphatidyl ethonolamine methyl transferase to phosphatidyl choline. In 1967, Danysz (7) reported an experiment by which animals were injected intraperitoneally with either Deanol or control saline for 23 days. The animals were sacrificed at different times during the

course of the experiment. Results showed a dose-related increase of brain acetylcholine peaking between 11 and 14 days in the Deanol group of animals with a gradual decrease to control levels by the 23rd day of the experiment.

Later, in 1975, studies by Haubrich (8) showed that the administration of Deanol (DMAE) to rats caused an increase of both choline and acetylcholine in the corpus striatum.

It is of interest to note that, in 1974, Silbergeld and Golberg (9,10) pointed out that lead induced hyperkinesis and MBDS share characteristics in common, both pathologies being associated with inhibition of cholinergic activity and responding similarly to pharmacological intervention. Working with an animal model of lead-induced hyperkinesis, they reported Deanol and Methyphenidate equally effective in controlling lead-induced hyperkinetic activity. In 1978, Jenden (11) reported that the administration of Deanol, 1000 mg. orally, to a normal individual resulted in increased levels of choline in plasma and RBC's.

From a biological point of view, it is clear then that the pathways for the transformation of DMAE into acetylcholine exist and that DMAE is indeed an indirect precursor of acetylcholine in brain tissue.

Clinical data on Deanol

Based on a number of publications from the 1960s, the Drug Efficacy Review Report by the National Academy of Sciences / National Research Council judged Deaner® (DMAE) as "Possibly Effective" for a variety of indications which can be grouped under the ADHD name. This report refers to the opinions of two (unidentified) consultants as follows:

Consultant #1 discussed 6 double blind studies (12 to 18) and judged Deaner to be "Effective"
Consultant #2 discussed 4 double blind studies (12,14,15,18) and judged Deaner to be "Possibly Effective"

It is of interest to note that both consultants' reviews were based on partially the same data (references 12,14 and 15).

Subsequent to the studies mentioned above, Lewis and Young (19) reported on a double blind, randomized, placebo-controlled comparative study of Deanol acetamidobenzoate and methylphenidate hydrochloride. The patient population consisted of 74 children between the ages of 6 and 12. There were 63 boys and 11 girls. Parents gave informed consent on behalf of their children. Inclusion criteria to participate in the study were poor school performance and a full-scale IQ on the WISC of 80 or above. Exclusion criteria included epilepsy, major neurological disease and psychiatric illness. 49 children had a

medical history of hyperkinetic behavior, 22 children demonstrated hyperkinesis during testing, 25 children had "soft neurological signs" and 17 had electroencephalogram abnormalities. Prior to, and at the end of the study period, the following examinations and tests were performed: Medical History and Complete Physical and Neurological examinations, Electroencephalogram, Blood tests: complete blood count, alkaline phosphatase transaminase and urinalysis. Psychological tests: Wechsler Intelligence Scale for Children (WISC) /full scale IQ, Visual Sequential Memory sub-tests from the Illinois Test of Psycho-Linguistic Abilities, Bender-Gestalt test Draw-a-person test and reaction time measure, Werry-Weiss-Peter scale as rated by the children's parents.

Experimental design : the protocol called for a double blind, randomized, placebo-controlled design by which children entered into one of three treatment regimens: Placebo, Methylphemdate or Deanol.

All the children took four identical capsules daily. For the initial two weeks of the study the dosage of methylphenidate was 20 mg. daily and for Deanol, 250 mg. daily. For the subsequent 10 weeks of treatment, methylphenidate was increased to 40 mg. daily and Deanol to 500 mg. daily.

Results : both treatments were significantly better than placebo at $p< 0.01$ on the WISC and full-scale IQ as well as on the reaction time task. Improvement for both treatments over placebo was at *5%* level in the Bender-Gestalt tests. The Visual Sequence memory and Draw-a-person tests did not show significant differences.

Comparing the two treatments using a Tukey HSD test, the methylphenidate group improved more than the Deanol group in the WISC and full-scale scores while the Bender-Gestalt perceptual test improved more with Deanol.

Adverse effects: one child receiving methylphenidate showed appetite loss and his dosage was decreased from 40 to 20 mg. One child on methylphenidate developed "freezing" of posture and behavior on methylphenidate, 40 mg. The adverse effect resolved at a lower dose. Parents of four children on methylphenidate complained that the children's appetite had decreased over the period of the study. There were no complaints or adverse effects in the Deanol group of children. The authors concluded that these results indicate that deanol, given to children with minimal brain dysfunction in doses of 250 to 500 mg per day over several months, can induce changes in a number of behavioral measures of approximately the same magnitude as the widely used methylphenidate.

Personal Experience

Over many years of clinical practice , I have had the opportunity of using Deaner (DMAE) to manage children with behavior and learning difficulties. The prescribing of medications in these situations comes only after careful consideration of the home and

school conditions as well as after adequate medical evaluation to rule out other pathologies. Within such considerations, my experience with Deaner has been very rewarding both in terms of efficacy and safety. Of course my observations were made in a clinical setting and have no corresponding parallel controls. Nevertheless, the overall response to a treatment program that included Deanol was generally favorable when compared with historical control measurements.

It is my considered opinion that Deanol is a safe (first of all, do no harm!) and effective option in the management of children with ADHD.

Conclusions

1. There are strong experimental data to show that Deanol is indeed a precursor of choline and brain acetylcholine.

2. Clinical experience accumulated over four decades indicate that Deanol would be beneficial in the management of children with ADHD, including improving attention span, focus and learning ability. Although some clinical trials have not shown a clear cut Deanol effect, such is not at all unusual in clinical research, and it is specially so when one has to rely on subjective testing. On the other hand, there are several study reports among those evaluated by the National Academy of Sciences consultants showing favorable results associated with the use of Deanol (DMAE).

3. The data generated by Lewis and Young under carefully controlled experimental conditions clearly indicate that Deanol (DMAE) in dosages ranging from 250 to 500 mg. per day resulted in statistically significant superiority of Deanol over placebo.

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Materials Sent To Dr.Osvaldo Re

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.

2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.

3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)

4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.

5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application

6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)

7. FTC, Dietary Supplements - An Advertising Guide for Industry

8. Lewis J, Young R. Deanol and methylphenidate in minimal brain dysfunction. *Clin Pharmacol Ther*. v. 17. n. 5. p. 534-40

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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

Joseph A. Sandford, Ph.D.

I have been asked to provide an opinion regarding advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler.

The FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

I received information and studies from counsel to Natural Organics (see attached list) and also conducted a review of a number of both published and unpublished investigations involving the effectiveness of dimethylaminoethanol (DMAE) in improving psychological functioning. Case studies, clinical trial studies and double-blind control studies were considered. Three studies were selected for a more in-depth evaluation. These three studies were chosen because they were published in peer-reviewed journals and utilized double-blind techniques to avoid researcher bias.

The first study by Muphree et. al. (published in Clinical Pharmacology and Therapeutics vol. 1 no. 3) was a double blind comparison of Deanol given in the form of an acid titrate salt tablet. The title of this study was 'The Stimulant Effect of 2-dimenthyaminoethanol (Deanol) in human volunteer subjects.' A lactose placebo was

used. Efforts were made to be sure that the tablets tasted the same and that individuals taking these substances could not identify the difference based on the bottles or other factors. The dose level based on other studies was relatively low and ranged from ten to thirty milligrams per day. Thirty-five second year medical student volunteers randomly divided into 2 groups comprised the subject pool. The reported benefit based on subjective responses relevant to attentional functioning was better mental concentration.

The findings were reviewed in detail in terms of the statistical significance. Rating scales were used to assess mental concentration. Seven out of seventeen (41%) of the subjects on Deanol rated themselves as 'improved.' Each subject made multiple ratings during the first two weeks of the study. It was reported that most of the improvements in mental concentration occurred after taking Deanol for two weeks. There were only two reports from individuals in the placebo group regarding an increase in mental concentration. It is noteworthy that on five occasions subjects in the placebo group rated themselves as experiencing a decrease in concentration, but no one in the Deanol group reported any decrease. The statistics used was a Chi Squared and the results were found to be significant at the $p<.02$ level. Based on these findings, it does appear that the conclusion by the researchers that Deanol did improve mental concentration for a number of individuals was supported.

The type of subjects used in this study was judged to be very high functioning given that they were second year medical students. It is noteworthy that no unusual degree of side effects or problems was reported by any of the subjects. All medical laboratory tests conducted did not disclose any gross changes from normal functioning that would indicate any concern or risk for the use of Deanol for almost all young adults. Any statistical improvement in this type of group by itself would not be likely to be found by chance alone unless there was not some type of active component and benefit from taking Deanol. It is not clear exactly how much mental concentration actually improved in a functional sense at this relatively low dose. It is this examiner's opinion that the changes obtained were subtle but noticeable by the mental students and are likely to be due to feelings associated with being more mentally alert. Thus, I do consider these researchers' conclusions to be valid.

A second study titled "Deanol and Methylphenidate in Minimal Brain Dysfunction" by Lewis and Young (1975) was reviewed. The subjects included seventy-four children between the ages of six and twelve referred by either their pediatrician or teacher because they were judged to be performing academically below their potential in school. The researchers noted that many of these children were also described as hyperactive. Individuals with Borderline or Intellectually Deficient IQ scores, major neurological problems or psychiatric illnesses were excluded. Deanol, methylphenidate and a placebo were administered using a random double-blind procedure so that neither

the experimenter nor subjects knew who was taking what medication or if they were taking a placebo instead. Deanol and methylphenidate were administered during the course of a three-month period. The subjects who took methylphenidate started off at 20mg daily and were increased after two weeks to 40mg daily for the next ten weeks. The participants in the Deanol group began at 250mg daily and this was increased to 500mg a day for the last ten weeks of the study. The hyperactive and non-hyperactive children were uniformly distributed among the three test groups. While this subject population was not well defined, the researchers noted that subjects were selected in this way in order to evaluate the type of children typically seen in general medical practice with learning problems. What is now diagnosed as ADHD, was originally labeled in the past Minimal Brain Damage and then later Minimal Brain Dysfunction. Based on this examiner's clinical experience the prevalence of the neurological problems in this group was higher than might typically be found in children now diagnosed as having ADHD. However, given that there is still much debate over the spectrum of behavior that falls within the diagnosis of ADHD, the study is still highly relevant to an examination of the substantiation of the claims as issue for Pedi-Active A.D.D.

The effectiveness of Deanol and methylphenidate were evaluated using several instruments. The tests, which are considered by this examiner to be relevant in assessing ADHD type symptoms, included the Wechsler Intelligence Scale for Children (WISC, first edition), Werry-Weiss-Peter activity rating scale and a reaction time test. Three other tests performed included a visual memory test, the Bender-Gestalt Figure Drawing Test and the Draw-a-Person Test. The other tests were not judged by this examiner to be particularly sensitive to any improvements in ADHD-type symptoms. Thus, the analysis of the test results was focused on the first three relevant tests selected above.

Based on the results reported in the WISC III manual, which is the latest version of the WISC intelligence test, it is clear that most individuals with a diagnosis of ADHD fall in the middle of the Average range. Their problems were noted based on sub-tests in the IQ test battery to occur due to deficits in mental processing speed and verbal memory. Both of these tasks are interpreted as reflecting problems that individuals with ADHD have due to deficits in working memory.

An improvement in intelligence testing when re-testing is completed in six months or less needs to be very carefully evaluated. The practice effect that is documented in the reliability section in the WISC III manual indicates that on re-test most individuals will show a seven to eight point increase in their Full Scale IQ when there is a short interval in between tests. For children in the six to seven age ranges it was found that the Verbal IQ test score improved about two points and that the Performance IQ score improved about eleven points. For the ten to eleven age range group an improvement of about two points was also found on the Verbal IQ test and for the Performance IQ score, a thirteen-point

increase was observed. In the fourteen to fifteen year old age groups an improvement of about three points was noted on the Verbal IQ and a twelve-point increase was found on the Performance IQ. Thus, an average increase of about two to three points will typically be found when the Verbal IQ test is re-administered and an increase of about twelve to fourteen points will be found for the Performance IQ. The reason for the larger increases in test scores of the Performance IQ in comparison to the Verbal IQ is due to the fact that higher scores can be obtained on a number of performance sub-tests if you complete them faster. Hence, practice leads to faster completion of a number of Performance IQ sub-tests and, thus, higher IQ scores are achieved.

For the Deanol group a 4.6 mean increase in the verbal IQ was found and the Performance IQ score improved by 11.2 points on the average. The methylphenidate group showed an increase of 8.2 points in their mean Verbal IQ test scores and a 17.9-point average increase in their performance IQ. It is interesting to note that the placebo group achieved only a 0.5 mean increase in their Verbal IQ test scores and a 4.4 increase in their Performance IQ test scores. Thus, the group, which did not receive any treatment, did not show the improvement that would normally be expected in IQ re-testing. In other words they did not function as most other 'normal' children do when re-administered the WISC test. In contrast, both the Deanol and methylphenidate groups demonstrated a significant increase in IQ test scores. These findings suggest the strong possibility that these treatment approaches potentially improved the children in this study so that they were able to function more in the 'normal' range in terms of learning from their past experiences and improving in their test scores, as a result.

A statistical test was completed to compare the treatment group and the placebo group based on the changes in the WISC scores for the Full Scale IQ. This statistical test found that the placebo group differed from both treatment groups significantly at the $p<.01$ level. Further statistical comparison of the Deanol group and the methylphenidate group separately to the placebo group also found a significant difference at the $p<.05$ level. In addition, the methylphenidate group was found to improve more that the Deanol group for the WISC Performance and Full Scale IQ test scores ($p<.05$). Thus significant changes were found specific to both of the active treatment groups with the Methylphenidate group showing stronger effects. It is important to note that IQ was not actually changed, but that the two treatments were facilitating the young subjects capability to show what they know.

An interesting test of reaction times was also included in this test battery. One hundred trials were completed requiring a response to the signal light, which was presented, intermixed with thirty random distracting stimuli that included a blinking light, a buzzer or both of these distracting stimuli. This test is similar to the Gordon Diagnostic System, which requires a child to push a button to target stimuli, while ignoring visual

distracters. The Gordon Diagnostic System was one of the first computerized cognitive performance tests used in diagnosing ADHD and is still used by some clinicians today. Typically, in continuous performance tests, both errors of omission and commission are reported; however in this test only reaction time was scored. In the placebo group there was only a 25-millisecond decrease in reaction time from pre- to post-testing. The placebo group's reaction time averaged 638 to start and was 613 at the end of treatment. The Deanol and methylphenidate groups were observed to be higher to start with pre-test scores of 812 milliseconds and 734 milliseconds respectively. Their improvement in mental processing speed was much greater and was reported to significantly differ from the Placebo group at the $p<.01$ level. One of the characteristic problems of individuals with learning difficulties or inattention is often that they are described as slow learners and this is reflective of slower mental processing speed. Both treatment groups were found to significantly improve mental processing speed on this reaction time test. Individual comparison to the placebo group for the Deanol and methylphenidate groups was found to be significant at the $p<.05$ level

Werry-Weiss-Peter activity Scale includes thirty-one behaviors related to functioning during meals, watching television, homework, playing, and behavior both away from home and in school. Checking one of three categories, none, moderate or severe, is how the ratings are done. The parents of each child completed this activity rating scale. Generally, there is a 'regression to the mean' when parents or teachers complete a rating scale for the second time. For the placebo group a decline of a mean of 4.2 points from a pre-rating of problem behaviors (31.2 to 27.0) occurred. For the Deanol group a 10.1 decrease occurred in the rating scale totals, which declined from 36.4 to 26.3. The methylphenidate group declined from 33.6 to 16.9 in their ratings. This was an average decrease in this behavioral rating scale of 16.7. The researchers did report that these changes in behavior were significant at the $p<.01$ level when the placebo group was compared to both treatment groups. When individual group comparisons using Dunnett's t test for multiple comparisons were completed for the different group rating scales, the significant difference of both treatment groups from the placebo group was confirmed at the $p<.05$ level or better. While this particular rating scale is not typically used today in assessing ADHD symptoms, it appears it was selected to broadly measure problems in a wide variety of different environments.

No major side effects were reported for either the methylphenidate or Deanol group. Six children taking Methylphenidate did have minor problems related to appetite suppression. One child on Methylphenidate was reported to show problems of 'freezing' posture and behavior that was identified by researchers as 'Parkinsonian' in nature. Adjustments were made to this child's medication and these problems did not reoccur.

In summary, the findings of this study are very supportive of the potential of beneficial effects of Deanol. The significant increases in IQ test scores was considered in line with expected test-retest changes that would occur in normal individuals. The fact that the placebo group did not improve in their IQ test scores on re-testing was considered as a significant sign of their continued dysfunction. The treatment groups did appear to improve, as one would expect for individuals when re-administered IQ tests after short intervals. The activity rating scales that were selected by the researchers to measure general global functioning were also found to reflect more significant improvements in both the ~~drug~~ treatment groups in comparison to the placebo group; indicating generalization of treatment effects to 'real-life' functioning. Also, an objective reaction time test, which was considered similar to the Gordon Diagnostic Test that is still currently used in assessing ADHD, was found to reflect significant changes in improved mental processing speed for both treatment groups together and individually comparison to the placebo group. Thus, this study provides substantial evidence that both Deanol and methylphenidate are likely to improve behaviors associated with better performance on tests and faster mental processing speed. In addition, the benefits of these treatment approaches in significantly reducing the disruptive and off-task behavior of young children classified as having a broad range of learning and behavioral problems in school was also supported.

The third study reviewed was titled 'Deanol in the Treatment of Hyper-Kinetic Children.' The researchers were Coleman, et. al. (1976). This group of researchers reviewed numerous clinical studies of Deanol completed prior to 1976. These clinical studies found that Deanol was efficacious in the treatment of behavioral problems of children. It was also reported that Deanol increased attention span, decreased hyperactivity and enabled children to be more efficient in their test performance. These researchers also discussed a comprehensive review of the previous research completed by Connors (1973). Connors concluded that the better-controlled studies previously completed showed little or no benefit from Deanol. He went on though to note that the most promising use of Deanol would be in reducing hyperactivity, impulsivity and inattention. Based on his review of the research literature, he believed that Deanol needed to be studied in children for a period of at least three months and that the dose used needed to be a minimum of 300mg per day.

This third study was conducted using double-blind placebo controlled procedures in order to evaluate the effectiveness of Deanol when given to schoolchildren diagnosed as hyper-kinetic. The purpose of the study was to assess the clinical effectiveness of Deanol in a number of areas. The potential effects of Deanol for reducing behavioral problems outside of school, improving academic performance and in increasing scores on standardized tests was evaluated using double-blind procedures. Deanol was administered for a twelve-week period to fifty children who were referred for behavioral

problems that generally consisted of hyperactivity. Gradually, the Deanol was increased until a total of 500mg was administered daily. No adverse reactions were identified for any participants that needed any adjustment in the systematic titration of Deanol.

Several instruments and clinical procedures relevant to assessing ADHD-type symptoms were utilized. These included a psychiatric examination and clinical assessment, psychological tests and both parent and teacher rating scales. The psychological tests included the Wechsler Intelligence Scale for Children (WISC, first edition), the Wide Range Achievement Test (WRAT, first edition) and the Porteus Maze Test. The Connors' Teachers Rating Scales (40 items) and the Connors' Parent Rating Scale (93 items) were the standardized rating scales utilized in this study. Both the psychiatrist and the subject's teacher rated overall general improvement in several areas in order to assess possible clinical changes and functional improvements in classroom behavior, respectively.

While the group of subjects in this study was found to have an average IQ (mean = 100.1), their teachers generally rated scholastic performance of these subjects as very much impaired (mean = 3.6 on the 1 to 4 point scale). Parents rated their children as having mild to moderate academic problems on an equivalent scale (mean = 2.5). Statistical test were completed to make sure that the two random assigned groups did not initially differ in any relevant way in terms of their physical characteristics or in respect to their test or rating scores.

As noted, the psychiatrists and teachers were not aware as to whether a particular child was receiving Deanol or a placebo. The measures that were found to show the most significant changes in this study were the global improvement rating completed by the psychiatrists and the teachers. For the psychiatrists 17 out of 23 (74%) of the children in the Deanol rating group were rated as slightly to markedly improved. In comparison, only 11 out of 25 (44%) of those individuals in the placebo group were rated as showing any improvement whatsoever. A marked improvement was noted in five children in the Deanol group and in only one child in the placebo group. Given the small sample size a Chi squared non-parametric test was administered and was found to be significant at the $p<.05$ level for these ratings by psychiatrists. In the classroom setting, the teachers global rating of classroom behavior showed that 13 out of 22 (59%) of the children in the Deanol group were rated as 'better' in terms of their overall behavioral functioning. Only 6 out of 23 (26%) in the placebo group were so rated. It is interesting to note that teachers rated more children in the placebo group as showing worse behavior than better (10 vs. 6 or 43% vs. 26%) in terms of overall classroom behavior. The statistical difference for these two groups on this rating scale showed a strong trend with $p<.06$. Teachers also rated each child's attitude towards authority. Eleven out of Twenty-Two (50%) were rated as better in the Deanol group and only 4 out of 22 (18%) were rated as

better in the placebo group. These results of improvement in attitude towards authority statistically supported a trend ($p<.07$). The WISC subtest scores were not reported in any tabular format. The researchers did note that they were found to show no statistically significant differential treatment effect. Also, no significant difference was found for either the WRAT or the Porteus Maze Test.

The Connors' Teacher Rating Scales showed for the placebo group a 'regression to the mean' in that the teachers statistically rated less problems in terms of both inattention and hyperactivity for the placebo group ($p<.01$.) The teachers also significantly rated less problems with inattention for subjects in the Deanol group. The improvement in attentional functioning was almost exactly the same for both the placebo and Deanol groups. A trend in the data ($p<.10$) was noted by the researchers that showed a larger reduction in the mean rating of hyperactive behavior for the Deanol group as compared to the placebo group. This trend indicated that Deanol might have some effect in reducing hyperactivity in children.

These test findings were supportive of the possible benefits of Deanol for some children, but were not conclusive by themselves. They did indicate that the benefits of Deanol may be mild and manifest in terms of a general global improvement in functioning based on the significant positive changes detected in the ratings completed by psychiatrists and teachers who participated in this study. The natural tendency for individuals involved in a study to rate symptoms lower when completing a second rating scale led to significant reductions in terms of inattentive symptoms and hyperactive groups for individuals in the placebo group. This effect is referred to as a 'regression to the mean.' It does appear though that the Connors' Teacher Rating scales indicated that Deanol might reduce hyperactivity. The failure to show clear-cut effects in this study may be due to the fact that Deanol is only effective for some individuals and not others, and is to be expected when dealing with any diagnosis that involves a wide variety of factors, as is true with ADHD. There was no indication that any of the children in the Deanol group became more dysfunctional, nor were any adverse effects reported for them. In conclusion this third study supports the potential benefit of Deanol for improving in a general way a child's psychological and behavioral functioning.

In conclusion, it is my expert opinion that these studies taken as a whole strongly indicate that some children will benefit from taking DMAE, a dietary ingredient that is included in Pedi-Active A.D.D. The scientific research findings reviewed support the conclusion that significant improvements occurred after taking DMAE in the attention span, test-taking abilities, mental processing speed and self-control for children with ADHD symptoms and learning problems. When these types of positive changes occur they are likely to generalize to better school behavior and improved academic

performance. It is also my opinion based on this research that administration of this dietary supplement to children does not raise any safety issues.

Materials Sent to Dr. Joseph A. Sandford

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.
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Expert Witness Report Addressing the Substantiation of Claims Made for Pedi-Active A.D.D. Pursuant to the Federal Trade Commission Case In the Matter of Natural Organics, Inc., and Gerald A. Kessler

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I. Introduction

I have been asked to provide an opinion regarding the scientific substantiation for advertising claims made for the Pedi-Active A.D.D. dietary supplement product that are at issue in the Federal Trade Commission's (FTC) case against Natural Organics, Inc. and Gerald A. Kessler. I am a medical researcher and neuroscientist; I am the Cecil H. Green Professor at M.I.T. and Director of M.I.T.'s NIH-funded Clinical Research Center. I am also Professor of Neuropharmacology at the Harvard-MIT program in Health Sciences and Technology. A special area of research interest for me has been the effect of food constituents on the brain.

My understanding is that the FTC has alleged that Natural Organics' advertising has made the following claims about Pedi-Active A.D.D.:

1. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

2. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

3. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD [Attention Deficit/Hyperactivity Disorder];

4. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

5. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

As a scientific expert witness, I do not offer an opinion as to the meaning of the advertisements. It is my expert opinion that the likelihood that Pedi-Active A.D.D. will help some such children is adequately substantiated by scientific data relating to dimethylaminoethanol (DMAE), which has been the focus of my review. It is also my opinion that the product does not raise any safety issues. A list of the information I was provided for review is attached, as well as other studies I have cited in the report.

II. Analysis of Issues, Scientific Studies and Data

DMAE is a naturally occurring biochemical found in the brain and liver and present in some foods. DMAE is a bioavailable substance: when consumed via dietary sources, part of it enters, and is carried in the bloodstream, and is able to cross the blood-brain barrier. I have examined some of the clinical studies relating to DMAE (e.g., Lewis and Young, Clin. Pharmacol. Ther., 17:534, 1975; N. Coleman et al., Psychosomatics, 17:68-72, 1976), and find that they support the claims for Pedi-Active A.D.D.

The data from studies showing that some children with ADHD benefit from DMAE are further supported by publications that have examined the mechanism by which DMAE likely affects the level and relative composition of biochemicals found in the brain, particularly in areas of the brain that affect attention and learning.

Administration of DMAE can cause major and prolonged dose-related increases in plasma choline levels (Millington, McCall, & Wurtman, 1978) by being methylated to choline (3-trimethylaminoethanol), principally in the liver (Blusztajn and Wurtman, 1981, 1983). Inasmuch as the carrier-mediated uptake of plasma choline into the brain is not saturated at usual plasma choline levels (Pardridge & Oldendorf, 1977), this DMAE-induced increase in plasma choline enhances choline's uptake into the brain (Millington, McCall, & Wurtman, 1978) thereby increasing brain choline levels. This increase of choline in the brain raises the substrate-saturation of the enzyme choline acetyltransferase and increases the synthesis and brain levels of acetylcholine (ACh), which functions as an important neurotransmitter (Cohen & Wurtman, 1976).

The resulting increase in ACh release within the brain would be expected to improve certain memory and learning functions, particularly among people in whom these functions are deficient. This appears to be the cause of the positive impact of DMAE administration on attention and learning, as seen in the clinical studies. Increasing ACh would also be expected to enhance the dopaminergic neurotransmission mediated by another brain neurotransmitter, dopamine (Ulus & Wurtman, 1976; Millington & Wurtman, 1982). Dopaminergic transmission is widely believed to be deficient in some people with ADHD, hence there is a sound theoretical basis for anticipating that DMAE might have positive effects in people with ADHD, as well as in those with related deficiencies in memory and learning related to acetylcholine (ACh) levels.

However, at very high dosages administered intravenously in rats, DMAE has an additional effect on brain choline metabolism which might be expected to diminish cholinergic (and, indirectly, dopaminergic) neurotransmission: It competes directly with plasma choline for transport across the blood-brain barrier and into the brain (Millington, McCall, & Wurtman, 1978). This latter effect would tend to reduce brain choline levels, and thereby diminish brain acetylcholine synthesis, at the pharmacologic dosages used in the rat model.

The actual net effect that any dose of DMAE produces on brain cholinergic (and, indirectly, dopaminergic) transmission, in any individual, is the result of these two actions: low doses of DMAE might be expected to be quantitatively converted to choline, and thus only to enhance cholinergic transmission. However, larger doses might transiently exceed the capacity of the liver (or other organs) to convert the increased concentrations of DMAE to choline, and the remaining unchanged DMAE may decrease brain choline uptake and ACH synthesis. No direct experimental evidence exists to rule in or rule out this hypothesis, however. Similarly, it might be anticipated that there would be sizeable differences among individuals in the extent to which their livers rapidly transform DMAE to choline, or even, for any individual, significant day-to-day differences in this transformation, depending – among other things – on the availability in liver of the cofactors used to methylate DMAE to choline (folic acid; B12, pyridoxine). Hence there is also a sound theoretical basis for anticipating that while DMAE will work well, in some people, for some of the time, it won't be effective in all people, all the time.

III. Conclusion

DMAE, a major constituent of Pedi-Active A.D.D., can increase brain choline levels and thereby enhance the release of brain acetylcholine and dopamine, both of which can be important in the treatment of ADHD; memory and learning disorders; and difficulty in focusing. Because DMAE has two putative antagonistic effects on brain choline uptake, a small amount of DMAE may produce an increase in brain concentrations of choline with concomitant improvements in behavior, concentration and learning; whereas a high, pharmacologic dose may produce negative effects on behavior, concentration or learning, as a result of lowering the amounts of choline transported across the blood-brain barrier (BBB) by the competitive transport mechanism described on pages 3 and 4.

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Materials Sent to Dr. Richard Wurtman

1. Nature's Plus Advertising Materials on Pedi-Active A.D.D. attached to Complaint as Exhibits A, B, and D.
2. Dr. Osvaldo Re letter dated 3/24/75 to FDA, re Riker Laboratories, Inc. Submission in Support Request for Hearing.
3. Deaner Submission Part I (Data on behavior/learning and hyperkinetic disorders of childhood)
4. Deanol v. Placebo in Hyperactive Children: Final Report on Riker Study R – 546 – 058, J. Lewis, M.D., B. Lewis.
5. 48 Fed. Reg. 23307, May 24, 1983, Deanol Acetamidobenzoate; Withdrawal of Approval of New Drug Application
6. NAS/NRC Deanol Panel Review (incl. 2 outside consultants)
7. FTC, Dietary Supplements - An Advertising Guide for Industry
8. Lewis J, Young R. Deanol and methylphenidate in minimal brain dysfunction. *Clin Pharmacol Ther*. v. 17. n. 5. p. 534-40
9. Re, O. 2-Dimethylaminoethanol (Deanol): A Brief Review of its Clinical Efficacy and Postulated Mechanism of Action. *Cur Ther Res*, v. 16, n. 11, Nov. 1974.
10. Oettinger L. Pediatric Psychopharmacology, A Review with Special Reference to Deanol. 1977.
11. Murphree HB Jr, Pfeiffer CC, Backerman IA. The stimulant effect of 2-dimethylaminoethanol (deanol) in human volunteer subjects. *Clin Pharmacol Ther* 1960 May-June;1:303-10.
12. Coleman N, et. al . Deanol in the Treatment of Hyperkinetic Children. *Psychosomatics*. vol. 17, April/May/June 1976. p. 68-72
13. Geller S. Comparison of a Tranquilizer and a Psychic Energizer- Used in Treatment of Children with Behavioral Disorder. *JAMA*. 174(5): 481-484. Oct. 1 1960
14. Kidd P. Attention Deficit/Hyperactivity Disorder(ADHD) in Children: Rational for Its Integrative Management. *Alt Med Rev*. 5(5): 402-428. 2000
15. Blusztajn JK, Wurtman RJ. Choline biosynthesis by a preparation enriched in synaptosomes from rat brain. *Nature*. 1981 Apr 2;290(5805):417-8.
16. Blusztajn JK, Wurtman RJ. Choline and cholinergic neurons. *Science*. 1983 Aug 12;221(4611):614-20.
17. Ulus IH, Wurtman RJ. Choline administration: activation of tyrosine hydroxylase in dopaminergic neurons of rat brain. *Science*. 1976 Dec 3;194(4269):1060-1
18. Milington WR, Wurtman RJ. Choline and Physostigmine Enhance Haloperidol-Induced HVA and Dopac Accumulation. *Eur J Pharmacol* 80(1982):431-434.
19. Kidd PM, Phosphatidylserine (PS): A Remarkable Brain Cell Nutrient"

Report Addressing the Claims Contained in the Federal Trade Commission Complaint Regarding the Efficacy of Pedi-Active A.D.D.

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I. INTRODUCTION

I have been asked to provide an opinion as to whether the following claims for Pedi-Active A.D.D., marketed by Natural Organics, have been substantiated:

A. Pedi-Active A.D.D. will improve the attention span of children who have difficulty focusing on school work;

B. Pedi-Active A.D.D. will improve the scholastic performance of children who have difficulty focusing on school work;

C. Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD;

D. Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD; and

E. Pedi-Active A.D.D. will treat or mitigate ADHD or its symptoms.

Pedi-Active A.D.D. is sold as a nutritional supplement. I understand that the product contains the following ingredients and dosages.

Table 1. Composition of Pedi-Active A.D.D.

Ingredient	Original Suggested Daily Dosage (1-2 tabs)	Current Suggested Daily Dosage (6-8 tabs)
DMAE (2-dimethylamino-ethanol bitartrate)	50 - 100 mg	300 - 400 mg
Phosphatidylserine (PS)	10 - 20 mg	60 - 80 mg
Phosphatidylcholine (PC)	10 - 20 mg	60 - 80 mg
Cephalin (phosphatidylethanolamine)	6 - 12 mg	36 - 48 mg
Phosphoinositides	3 - 6 mg	18 - 24 mg
Palmitic acid (fatty acid)	4.5 - 9 mg	27 - 36 mg

Ingredient	Original Suggested Daily Dosage (1-2 tabs)	Current Suggested Daily Dosage (6-8 tabs)
Stearic acid (fatty acid)	1.5 - 3 mg	9 - 12 mg
Oleic acid (fatty acid)	2.5 - 5 mg	15 - 20 mg
Linoleic acid (fatty acid)	13.5 - 27 mg	81- 108 mg
Linolenic acid (fatty acid)	3 - 6 mg	18 - 24 mg

II. DATA BASE

Much of the material submitted by Natural Organics, the manufacturer/marketer of Pedi-Active A.D.D., was either very dated (e.g., chapters from old textbooks) or irrelevant to the questions at issue. For example, no obvious relevance can be found in references for thyroid abnormality in ADHD, for Ginkgo biloba, for ginseng extracts, for use of choline chloride in schizophrenia, for depression from choline, for reduced glutathione, for follicular hyperkeratosis, for cardiovascular disease, or for fatty acids (docosohexaenoic acid, gamma-linolenic acid) that are not listed in the ingredients of Pedi-Active A.D.D. Some of the material is relevant, and this was supplemented with additional literature searches, both by FTC counsel prior to my consultation and by me. My own search disclosed mainly animal literature, not very contributory. The most relevant materials pertain to the dimethylaminoethanol (DMAE), previously known as deanol and marketed as Deaner, which appears to be the pre-eminent and possibly key ingredient of Pedi-Active A.D.D. Those references are summarized in Table 2, which includes selections from original materials submitted by Natural Organics and additional material supplied by FTC counsel. The other main ingredient appears to be the aggregate list of phospholipids and fatty acids contained in Leci-PS, obtained from Lucas Meyer. Table 3 summarizes the studies of phospholipids and polyunsaturated fatty acids relevant to ADHD treatment, including a recent summary of two studies from Charles Gant.

Table 2. Reports of dimèthylaminoethanol (deanol) for ADHD/hyperactivity spectrum symptoms. Deaner was dimethylaminoethanol acetamidobenzoate.

Author	# Ss, age, Selection	Dose/ day (mg)	Design, duration	Measures	Results	Comment *
Pfeiffer, 1957	Mice & diverse human epileptic	250–>50 mg DMAE bitartrate	Various open	Clin. impress, seizures	DMAE raises emotionality; petit mal seizure threshold.	Halves GM seizure threshold.
Oettinger, J. of Pediatrics 1958	17 epileptic, 108 others, age 6mo-20yr. Beh problems, poor response to other drugs	20-200 mg, mode 50 mg	Open trials 1-9+ mo.; chart review	Global impression by clinician ; BP, blood, urine. Bender, DAP	48% good, 20% fair, 20% no change, 12% worse; no toxic effects noted	Poorly controlled: no placebo, variable duration. Hard to interpret
Murphree et al, 1959?	35 normal adult volunteers	10-30 mg deanol tartrate	DB parall D vs. placebo, 12 wk	Questionnaire, nonsense words, physiological, Rorschach	Better sleep, incr. muscle tone. Small effect concentration	Confusing data, weak effects; ? of lactate>tartrate
Geller, 1960	75, age 5-12 Hyperactive, aggressive, poorly integrated	100-->150 mg Deaner	25/grp parall, DB placebo, trimeg-lamide comparator 3 mo.	Structured observations, history	Deanol better for puzzle solving, clear speech, purposeful activity	No statistical significance test; archaic technology, concepts
Fields, 1961	400, age 2-19 CNS, endocr, psychoses. 200 had endocrine d/o All tx'd with thyroid, pituit multivitamins	25->100 mg daily Deaner. (deanol acetamido-benzoate)	Open trial, no controls, 10 months	Clinical impression of MH, behavior, ability, sleep, alertness, eating habits. IQ for 10 Ss	Improved eating, sleeping, alertness, concentration, lower tension, apathy, agitation, irritability. 70% "excellent." 10 Ss constipation or restlessness SE	No controls for 10-mo attenuation. Endocrinol..& neurologically abnormal sample. Can't generalize ADHD or nl.
Huddleston et al, 1961	120, element. to college age Reading D/O	150 mg daily	DB match parallel D & Pl 8 wk.	Gates Reading Test, Clerical speed&accuracy	No diff. reading; signif. diff. cleric speed & accuracy	no means, no ES
Fleming & Orlando, 1962	50, mean 18yr, institutional MR, IQ av 54	75->150 mg daily deanol	DB parallel, 92 days D&Pl	Reaction time (RT)	Did not improve RT, attn	Data puzzling, but nonsupportive

Author	# Ss, age, Selection	Dose/ day (mg)	Design, duration	Measures	Results	Comment *
Bostock & Shackleton, 1962	33, age 7-11 child guidance clinic, mild beh. problems	75 mg daily DMAE Deaner	open Tx 3-4 mo.	parent rating, Vigotsky Block Test, Tapping Test	8 got worse, 25 had scattered improvements	Possible practice effect. No means, sd. Unconvincing.
Kugel & Alexander,, 1963	42; age 6-13; IQ 78; CNS, behavior disorders	100 mg deanol acetamido-benzoate	DB Xover, 3 mo. each D & placebo	IQ, social, emotional scales; parent interview	No signif. Diff. deanol vs. placebo	Smaller children no better than large.
Jacobs, 1965	60, age 4-15; MR	deanol Deaner	DB Xover, 1 mo. with washouts	Tacher & parent ratings attention, alertness, tantrum	Negligible diff. ES 0.0-0.3	Dose unspecified, atypical sampl
Conners re Duncan Comparison (LSU) 1971, FDA, 1975, 1983	43; age 6-14, mean age 8.5; Pediatric neurology referrals	5 tabs Deaner , 500 mg/day	26-37 days DB Deaner, placebo, wait list	Ratings by P, T, neurologist (clin). EEG, CPT, visual recall	58% D, 10% P improved by clin. rater, no diff. by P or T. CPT trend. "No reliable Tx effects"	? re blindnes. Most tests no support for efficacy
Conners re Oettinger comparison, 1971; FDA, 1975, 1983	44 (or 46); age 5-13 (or 8-14); Behavior and academic problems	500 mg/day Deaner	DB 4 weeks parallel deanol vs. placebo	Ratings P & T; 7 psychological tests	Most tests n.s.; total T rating <.04; CPT omissions <.05	Weak suggestion of effect.
Lewis & Lewis, 1973 Riker	18 age 6-10 hyperactive	500 mg	cross-over w. placebo ABA/BAB 1 mo. each	P/T rating clin. rating self-esteem NP tests	Most measures n.s., ES <0.2; anxiety 0.3-0.4	Possible order effect; overanalyzed
Conners, 1973	Review. Child behavior disorders	Rec. individ. titration, 150-500 mg	Rec. >25 per condition	NP tests and subjective ratings	Problems with statistical analysis, subjects	Most studies with MR/DD
Millichap, 1973	239 in 6 studies; B&L problems (review)	10-1000 mg Deaner	4-36 weeks	various	47% improved; 3/6 studies negative	"deanol...of little, if any, value" for HA & LD
Re, 1974 Riker	Review article	Rec. 500-1000	Rec. 3 mo.		Crosses BBB; ? whether increases acetylcholine	AcCh levels rose, then fell with cont'd D. cites DiMascio

Author	# Ss, age, Selection	Dose/ day (mg)	Design, duration	Measures	Results	Comment *
Lewis & Young, 1975; FDA, 1975, 1983	74, age 6-12. Learning problems, 49 hyperactive.. Referred by T, counselors, pediatricians. Low school performance.	250 mg 2wk then 500mg deanol; 20–>40 mg methylphen-idate (MPH) daily	DB, 3 parallel groups: deanol, MPH, placebo, 3 mo.	WWP Behavior rating by P (Beh), WISC IQ, DAP, Bender, visual memory test, reaction time	Both drug groups improved cf. placebo, not signif. diff, but Beh pre-post change= 4 placbo, 10 D, 17 MPH; post IQ= 103, 110, 115	Weak cf. MPH (½-way betwn plac & MPH); placebo-contrd ES 0.1-0.6 cf 0.8-1.3 for MPH; Post Beh 27pl, 26 D, 17 MP
DiMascio & Finnerty, 1975 or 1973, unpublished **	50 age 6-12	300 escalated to 500 first two weeks Deaner	parallel, 25 each group: placebo, D 12 wk	P/T rating clin. rating NP, IQ, achiev. tests	Clin 0.05, others n.s.. ES small. Placebo better on reading, arithm. More D Ss better	signif. clin. rating due to 10/23 slight improvement Date contradiction
Coleman et al, 1976 ** FDA, 1975, 1983	50, age 6-12, HK behavior problems ref. by teachers, counselors, MH cntr, MDs 3-5 Sx CTRS	300 mg first wk, 400 2d wk, then 500 mg deanol	2 parallel grps: 25 each deanol & placebo, DB. 12 wk.	Behavior ratings by P/T, CGI, WRAT achievement, Porteus Maze, WISC IQ	CGI 7 D, 6 Pl with best rating; no diff. attn rating by teacher; possible diff. HA rating	Same data as DiMascio & Finnerty, 1973 & 1975
Oettinger, 1977	MBD review article	N.A.	N.A.	Opinion, HFD, Bender	Impression of effect	Lack of side effects
Saccar, 1978	Review: 303 MBD	Rec. 300 mg	various	various	Most studies either <MPH or amph., or =placebo	

* The column "comments" is not meant to be comprehensive; the studies are discussed in more detail in the later text.

** The Dimascio/Finnerty and Coleman et al studies appear to be the same subjects and same data, but with different details, and are referred to separately later in the report. The dashed line indicates the ambiguous distinction.

KEY: AcCH = acetylcholine; Bender = Bender Visual-Motor Gestalt Test; BBB = blood-brain barrier; BP = blood pressure; CGI = Clinical Global Impression; CNS = central nervous system disorder; CPT = continuous performance test; D = deanol, Deaner, or DMAE; DAP = Draw-a-Person Test; DB = double-blind; DD = developmental disorder; Dx = diagnosis; ES = effect size (number of standard deviations); HA = hyperactivity; HFD = Human Figure Drawing; HK = hyperkinetic; LD = learning disorder; MBD = minimal brain dysfunction; MH = mental health; MPH = methylphenidate (stimulant drug); MR = mental retardation; N.A. = not applicable; NP = NeuroPsychological testing; P = placebo or parent; P/T = parent & teacher; SE = side effects; Ss = subjects; T = teacher; Tx = treatment; WWP = Werry-Weiss-Peters behavior scale; Xover = crossover design

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Table 3. Selected reports of phospholipid (e.g., Leci PS) treatment relevant to ADHD

Author	# Ss, age, Selection	Dose/ day (mg)	Design, duration	Measures	Results	Comment
Gant, 1998	20 schoolage ADHD	mixed soy phospholipid mostly Phospha-tidylcholine.	Comparisn to MPH, 10 each group no placebo	11 CPT subscales Conners scale, grades	Both groups improved 5/11 CPT scales, Conners rating, "scholastic performance"	No placebo control. Doses? Blinding? Randomization? Details lacking
Gant, 1998	ADHD schoolage 10 Ss?	1-3 g phospholipid & fatty acids, targeted supp	Open trial, no controls	similar to above	"outcomes excellent" with no specification. RCQ & ACQ pre-post $p<0.001$	Uncontrolled. Contradictory rationale for supplementation
Kidd, 1999 (letter to Crook): Kunin study & #3741	5, age 3-6 attentional problems (ads)	200 mg Phospha-tidylserine (PS) from Leci-PS	Open trial, no controls 6 weeks	finger tapping, clinical impressn, testimonial	3/5 "significantly improved" by testimonial. No adverse effects	Dimensional data lacking; preschool
Kidd, 1999 (letter to Crook): Ryser study	12, age 7-19 ADHD, pre-existing diagnosis	100-200 mg (300 mg for 15-yr-old) phosphatid-ylserine from Leci-PS	Open trial, no controls 12 weeks; Previous Tx contind	Clinical impression, chart review	9/12 "clear benefit" beyond BL drugs & EFA suppl. Calming Improved concentr., attn, mood, memory. No side effects.	Dimensional data lacking. No statistical test., no plac.; Incl. teens. Rec. 300-500 mg forODD

KEY: ACQ = attention control quotient; CPT = continuous performance test; EFA = essential fatty acids; MPH, methylphenidate, a stimulant drug; ODD = oppositional-defiant disorder; RCQ = response control quotient, measure of impulse control.

III. ADHD/ADD AS A DISORDER: DESCRIPTION, ETIOLOGY, COURSE, DIAGNOSIS AND TREATMENT

A. General Description

Attention-deficit/hyperactivity disorder (ADHD), also known as attention-deficit disorder (ADD), is the most commonly diagnosed behavior disorder in North America, occurring in 3-8% of school children and smaller proportions of adults. It is a chronic syndrome of age-inappropriate inattention, distractibility, impulsivity, and restless overactivity. In children it has a male preponderance of 2:1 or 3:1 in epidemiologic samples, higher in clinical samples. In adult-diagnosed samples, the sex ratio may approach equality.

In November, 1998, to summarize the accumulation of scientific findings and resolve some of the public controversy, the National Institutes of Health (NIH) held a 3-day consensus development conference. A panel of experts from outside the ADHD field but who had requisite

expertise in evaluating scientific evidence listened to and read reviews of each topic area by national ADHD experts and critics. One of the foremost critics of the concept and its main treatment was an invited presenter, and other critics who requested it were given an opportunity to present their views and any evidence supporting their criticisms. The panel drafted a summary report, which was presented to the assembled investigators, clinicians, and critics for comment and was then revised. It concluded that ""...there is validity in the diagnosis of ADHD as a disorder with broadly accepted symptoms and behavioral characteristics that define the disorder." (National Institutes of Health, 1998b). This conclusion was based on the following considerations:

1 The diagnosis is reliable, with roughly the same prevalence across cultures and continents when the same criteria are used (Bird, 1998).

2. Though (as with other mental disorders) there is not a simple biological test pathognomonic for the diagnosis, there are converging lines of evidence for a biological basis (Swanson & Castellanos, 1998).

3. Patients with stringently diagnosed ADHD have impairments across a wide range of functioning and settings (Hinshaw, 1998).

4. There are frequent comorbidities, and both ADHD and its comorbidities tend to be chronic (Barkley, 1998).

5. The disorder affects not only the patient, but also parents, sibs, peers, and school staff (Forness, 1998).

These five points are elaborated below after a historical divergence into nomenclature and concept development.

B. Names, Concepts, and Diagnostic Terms over Time

The syndrome has been known for over a century. Early names included Still's syndrome, Strauss syndrome, and hyperkinetic impulse disorder or hyperkinetic syndrome, still preserved in the International Classification of Diseases (ICD-10) name for the disorder. Because the most severe early cases were associated with such biological risks as Von Economo's encephalitis, complicated gestation or delivery, head trauma, mental retardation, seizures, etc., it was for awhile considered a sequela of brain damage. When the same symptoms were noted in some children without such an explanatory history, the term "minimal brain damage" or "minimal brain dysfunction" (MBD) came into vogue to indicate that we suspected something was wrong with the brain but couldn't demonstrate it by the tests available at the time. "Minimal cerebral dysfunction" was also occasionally used.

The original American Psychiatric Association Diagnostic & Statistical Manual (DSM) did not recognize the disorder. DSM-II (DSM Second Edition, 1970) used the term "hyperkinetic

reaction", implying that it was a reaction to some stress or pathogen (without evidence to support the imputed causality). Eventually the hybrid Greek-Latin term "hyperactive" crowded out the all-Greek "hyperkinetic", with such names as hyperactive child syndrome. Up to this point, the naming had been based mainly on the obvious motor restlessness and to some extent the impulsiveness, but experts were recognizing that the attention deficits were of at least equal importance, and perhaps more basic. In 1980 DSM-III promoted the attention deficit to pre-eminent billing with the new name "attention deficit disorder", with (ADDH) or without (ADD) hyperactivity. This term –ADD– persists in many circles, is still preferred by many educators, and is preserved in the names of such self-help organizations as ChADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder) and ADDA (National Attention Deficit Disorder Association). DSM-IIIR resurrected hyperactivity with the name "attention-deficit hyperactivity disorder" (ADHD), attempting a unitary concept by merging symptoms of attention deficit, hyperactivity, and impulsivity in a single symptom list of criteria. DSM-IV (1994) preserved this name, but, based on data analyses, separated out the inattention from hyperactivity-impulsivity, and allowed diagnosing subtypes with either set of symptoms. At this time the acronyms ADD and ADHD are often used interchangeably. Though the currently official term is ADHD, parents, support groups, educators, and other professionals generally recognize ADD at least as well as ADHD.

While the current name emphasizes attentional deficits and overactivity, we should note that impulsiveness (motor, verbal, and mental) may be the most central and unifying symptom theme. The lack of reflectiveness and other executive function is pervasive. Patients with the disorder may act before they think, react before they think, speak before they think, and even think before they think, jumping to conclusions prematurely. The impulsiveness may be associated with impatient seeking of sensory input and other reinforcement; there is some evidence that patients with ADHD do not find ordinary activities as inherently rewarding as do most age mates.

C. Diagnostic Criteria, Reliability, Validity, and Cross-cultural Prevalence

Table 4 shows the current diagnostic criteria, taken from DSM-IV. Note that, in addition to the full-blown disorder, the combined type, it is also possible to diagnose a partial expression, either the inattentive type or the hyperactive-impulsive type, each of which does not meet criteria for the other partial type. The combined type, of course, meets criteria for both of the partially expressed types. Prevalence would vary according to whether only the combined type or all 3 types are counted. Note that an essential part of the criteria is the chronicity of the behavior pattern, which must be present at least 6 months and begin before age 7. Note also that the symptoms must be causing some impairment in home, school, or peer functioning. ICD-10 criteria for hyperkinetic syndrome are similar but more stringent, approaching what in DSM-IV would be considered ADHD combined type as reported by both parent and teacher (Lahey & Willcut, 1998).

Both structured interviews and scalar instruments have demonstrated high reliability, and show validity in predicting independent clinician diagnosis, actometer readings, performance on neuropsychologic tests such as continuous performance test (CPT), objective systematic behavioral observations, underachievement, and later outcome (Lahey & Willcut, 1998).

Table 4. Diagnostic criteria for Attention-Deficit/ Hyperactivity Disorder from DSM-IV

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Inattention
(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often-avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity/impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Hyperactivity
(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively
Impulsivity
(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria Al and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion Al is met but Criterion A2 is not met for the past 6 months (Roughly equivalent to DSM-III ADD)

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion Al is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" Should be specified.

314.9 Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified

This category is for disorders with prominent symptoms of inattention or hyperactivity-impulsivity that do not meet criteria for Attention-Deficit/Hyperactivity Disorder.

The symptoms listed in Criterion A of Table 4 above are generally well known, implied by the names of the disorder. Terms like "difficulty paying attention" and "does not follow instructions," as noted in exhibits A and B of the FTC's complaint, appear close to wording in the DSM-IV symptom list below, and "inability to remain focused," also in the exhibits, seems to restate in different words the DSM-IV symptom "difficulty sustaining attention". Parents and teachers often use such terms in describing a child with ADHD, in addition to such descriptors as "not working up to capabilities" and "does not work well with others," also noted in exhibits A & B. Conscientious parents are also likely to report much family stress around homework, as implied in the exhibit A language "...yelling, begging and pleading doesn't get your child to do their homework..." Most clinicians who hear a description of child behavior with such terms will suspect ADHD, though the diagnosis requires much more evaluation, including ruling out other mental disorders as the cause of the symptoms.

A review of epidemiologic studies from 15 countries on 5 continents over the past 15 years using a variety of definitions of the disorder found strong support for the cross-cultural validity of the syndrome despite prevalences ranging from 1% to 20% across cultures. Though part of the variance is undoubtedly due to setting and culture (largely through a cultural informant effect), Bird (1998) concluded that the "differences may be more a function of the diagnostic system..., methods of ascertainment, and other methodological artifacts." The syndrome itself showed high internal consistency across cultures and settings, for example, on factor analyses of diagnostic instruments, which repeatedly yielded two robust factors of inattention and hyperactivity-impulsivity. Another example is the finding in a Chinese sample of the same neuropsychological test deficits, actometer readings, and history of biological risk factors and developmental delays as reported in Western

samples. Despite some cultural informant differences, a stringent consistent definition yields reasonably consistent prevalence across cultures. Bird (1998), reviewing all the available data estimated the worldwide prevalence of the DSM-IV diagnosis at about 4-5% in middle childhood.

D. Biological Basis and Etiology of ADHD

While causation and pathogenesis have not been completely defined, converging lines of evidence make a convincing case for a biological basis in the vast majority of cases. One of the best documented and pervasive causes is a genetic vulnerability for many, perhaps most, cases. Many family studies, twin studies, and adoption studies have consistently reported high heritability, usually over 0.5, sometimes up to 0.8 (1.0 would be completely heritable, with no contribution of environment). Though specific genetic mechanisms have not been definitively documented, two dopamine genes have been reported to be associated with the disorder: the dopamine transporter gene (DAT1) and the D4 dopamine receptor gene (DRD4). Preliminary hypotheses are that: 1) the 10-repeat allele of DAT1 on chromosome 5p15.3 results in too rapid re-uptake of dopamine, and 2) the 7-repeat allele of DRD4 on chromosome 11p15.5 results in dopamine receptor hyposensitivity (Swanson, 1998). Both of these hypotheses would be compatible with the dopamine-deficiency hypothesis of pathogenesis, which was suggested by the fact that most drugs that are beneficial for the disorder enhance dopamine neurotransmission (Swanson, 1998). However, it does not appear that the two genes identified thus far account for the degree of heritability found in family studies.

Four independent groups of investigators using anatomical magnetic resonance imaging (MRI) have convergently found ADHD brains smaller than controls in the frontal areas (especially right), and basal ganglia (especially caudate nucleus). Such findings are compatible with neuropsychological tests showing impairment of executive function (planning, inhibition of impulse, voluntary direction of attention) subserved by the frontal lobes and attentional systems depending on the basal ganglia. Unfortunately, other brain imaging strategies, such as positron emission tomography (PET), have not yielded the same consistency of results, so it is not possible yet to draw any conclusions from such functional studies as PET, single proton emission tomography (SPECT), and functional MRI (Swanson, 1998).

Besides genetic vulnerability, numerous environmental and indirect pathophysiologic etiologies have been reported to cause symptoms of inattention and/or hyperactivity in animals or humans, at least in small subpopulations. In addition to the encephalitis, birth trauma, cranial anomalies, mental retardation, etc. associated with the earliest recognition of the syndrome, more recent reports suggest heavy metal poisoning, mineral deficiency, specific essential fatty acid deficiency, specific food component sensitivities/allergies, thyroid abnormality, and pediatric autoimmune disorder associated with Group A beta-hemolytic streptococcal infection (Arnold, 1998, 1999). (The weight of evidence for these imputed causes varies widely, often with inconsistent or sparse documentation. See the "Treatment" section for more details.) Probably no one of these potential causes is important in more than a small minority of ADHD cases and most account for only single-digit percentages (e.g., thyroid abnormality may be as low as 2%), but in the aggregate they appear to contribute substantially to a considerable proportion of cases of ADHD.

Further, they may be compatible with the genetic and brain imaging findings above (e.g., some of the heritability may result from inheritance of immune disorder or thyroid dysfunction; heavy metal poisoning, viral exposure, or nutritional deficiency might impair growth of specific brain regions; or deficiency of zinc, necessary for optimal dopamine function, might further stress an inherited borderline DRD4 status).

As with most neuropsychiatric disorders, stress aggravates the symptoms. Overwhelming stress, resulting in post-traumatic stress disorder or major depression, can even mimic many symptoms of ADHD. Hyperactivity has been reported as a sequela of maternal deprivation. It is likely that the development of clinical symptoms results from interaction of genetic vulnerability with environment, both physical/chemical and psychosocial.

While patients with ADHD show consistent neuroanatomic, neurophysiological, neuropsychological, and other biological differences from normal controls *at the group mean level*, those differences are not specific and consistent enough to be used as diagnostic tests for individual patients at this time. This situation is the same as for most neuropsychiatric disorders: for example, major depression shows measurable alterations in adrenocorticoid regulation at the group mean level that is not useful as an individual diagnostic test. Similarly, schizophrenia shows smaller size of some brain structures compared to normal controls at the group mean level, but because of wide individual variation, brain scans are not currently useful diagnostically for individual patients with schizophrenia. Thus the lack of an individual biological test for ADHD is not a compelling argument against the validity of the diagnosis. Despite the efforts by some critics to discredit the diagnosis, the vast majority of clinical scientists recognize ADHD as a valid diagnostic concept in the process of refinement.

E. **Impairments from ADHD:**

The deficits in attention, impulse control, and activity modulation cause secondary impairments in many domains of function. This occurs not only in clinical samples, where one would expect impairment, but also in epidemiological samples. Further, even if diagnosis is made without requiring the impairment criteria C and D shown in Table 4, those meeting the other diagnostic criteria show significant impairment, demonstrating that it is not mere circularity from the DSM-IV diagnostic criteria. Finally, impairments are chronic, persisting into adulthood.

One of the most important domains of impairment is peer status. The intrusiveness and sometimes aggression resulting from the hyperactivity and impulsiveness, coupled with inattentiveness to social cues, may lead to difficulty socializing appropriately. Children with ADHD have a high rate of peer rejection, probably resulting from their impaired social skills.

Another functional domain affected is academic achievement and academic performance. (Achievement is what is actually learned as shown by individual achievement tests; academic performance is quantity and quality of schoolwork, on which grades depend.) Youngsters with ADHD typically underperform and underachieve even if they do not have comorbid learning

disorder, as perhaps 20-25% do. The combination of poor attention, distractibility, and disorganization understandably puts such a child at a disadvantage in school, and may lead to progressively more problems in the secondary schools, which require more self-organizational skills. Follow-up studies show that as adults, those diagnosed with ADHD in childhood completed less education than comparison control subjects (Johnston, 1998).

The parent-child relationship also suffers. Even prior to parental disappointment in school and household chore performance, parents may have been stressed by the preschooler's overactive impulsiveness. Stressed parents lead to stressed family relations and stressed children. Parents often in desperation drift into aversive or otherwise discordant parenting practices. There are high rates of marital discord and divorce compared to normal families. Divorce, of course, adds to stress level for both parent and child. Since any disorder, including ADHD, is aggravated by stress, a vicious cycle often develops in which the child's symptoms fuel family stress and family stress aggravates the child's symptoms (Hinshaw, 1998).

Even the domain of physical health may be impaired. The available research suggests a higher rate of accidents than control groups (Hinshaw, 1998). This includes a reported 4-fold rate of automobile accidents by adolescent drivers with ADHD compared to other adolescents. The possibility of accidental head injury suggests another potential interaction of cause and effect, since brain injury can cause or aggravate ADHD symptoms.

As adults, those who had an ADHD diagnosis in childhood, when compared to controls, have lower status jobs, more difficulty completing tasks, and higher rates of quitting and being laid off. They had lower social skills in simulated job interviews and heterosexual interactions. Adults with clinically diagnosed ADHD, compared to controls, have higher rates of marital problems, separation, and divorce. They appear impaired in child-rearing strategies and ability to co-parent (Johnston, 1998).

F. Comorbidities and Chronic Developmental Course

The symptoms of ADHD, especially the overactivity, tend to become less obvious with maturity, but in most cases do not leave completely. Just as normal individuals develop better impulse control, motor restfulness, and ability to focus and attend during successive developmental stages into young adulthood, so also do patients with ADHD. However, they tend to remain at some disadvantage to age peers in these areas, especially for attentional skills and reflectiveness. Of young children diagnosed, about 2/3 to 3/4 will continue to meet diagnostic criteria into early adolescence and 1/3 to 1/2 continue to meet criteria in late adolescence, with additional significant proportions continuing to have troublesome symptoms below the diagnostic threshold (Barkley, 1998). The frequent comorbidities of ADHD also tend to change over the course of development:

About half of children with ADHD also have oppositional-defiant disorder (ODD) or conduct disorder (CD) or both in succession. Approximately 1/4 to 1/3 of clinical samples of children with ADHD also have a diagnosable anxiety disorder beyond simple phobia. Comorbid major depression increases with age, especially among females with ADHD. One follow-up study

found a major-depression rate of 28% at age 20-30 (Barkley, 1998). The comorbid conduct disorder and later antisocial personality (diagnosable only after age 18) bring another common comorbidity: substance use in adolescence and adulthood. The risk of substance use disorder or dependence by adulthood ranges from 10% to 37% (Barkley, 1998).

Learning Disorder is academic achievement substantially below ability level not explained by poor schooling or other lack of opportunity or incentive. This underachievement, a deficit in what is learned, is distinguished from academic underperformance, a deficit in the completion of work, tests, quizzes, homework projects, class participation, and other things on which grades are based and which depend on adequate attention and focus. About 20-25% of children with ADHD (higher for inattentive type) have learning disorder beyond the problems of inattention. Many additional children with ADHD have academic underperformance.

G. Quantitative Disorder

The "symptoms" or "deficits" of ADHD are not pathognomonic nor qualitatively different from variations of traits or abilities found in all persons. Everyone has some ability to voluntarily direct attention but to be distracted by salient stimuli; and everyone has a preferred activity level with some reflex reactivity. The impairment (and hence disorder) arises from the consistent excess of activity, distractibility, and impulsive reactivity, analogous to hypertension, in which some blood pressure is normal, but too much (or too little) is impairing/pathological.

H. Diagnosis of ADHD

Though the diagnostic criteria in Table 4 may appear easy to follow, professional objectivity and experience is needed for valid implementation. A common pitfall for novices is to jump to a conclusion on the basis of some symptoms without considering all the criteria. For example, it is necessary to rule out the possibility that another mental disorder accounts better for the symptoms. The patients themselves often have little insight into their own problems, and parents may be too close and involved to judge objectively. For such reasons, a health professional experienced in diagnosing and treating ADHD should be responsible for making the diagnosis and advising the patient and family.

I. Treatments for ADHD

Dozens of different treatments have been advocated for ADHD, many with little or no objective, rigorous scientific support. Further, even the well-studied ones are not universally effective; there is no one treatment that is safe and effective for all cases of diagnosed ADHD. The two best-documented and most widely applicable treatments are psychoactive medication, especially stimulants, and behavioral treatments. These have demonstrated efficacy and safety for the majority of patients with ADHD in hundreds of well-controlled scientific studies.

For stimulant medication, there are hundreds of placebo-controlled studies showing a large benefit on group means, with an acceptable side effect profile and near absence of serious (life-

threatening) adverse events. About 2/3 of well-diagnosed patients who try a stimulant will respond satisfactorily, and if the remaining 1/3 try a second stimulant, about 2/3 of those will respond satisfactorily, for a nearly 90% favorable response overall (Arnold, 2000; Elia et al, 1991), with further patients responding to trials of other medicines, including antidepressants and alpha-2 agonists, in a "medication strategy" of treatment (MTA Cooperative Group, 1999).

Behavioral treatments also have hundreds of controlled studies, either with sham comparison treatment, wait-list controls, or ABAB designs (turning the symptoms off and on by alternating treatment with nontreatment). A moderate effect is noted on group means (Richters et al, 1995). About 3/4 of children with well-diagnosed combined-type ADHD can be maintained satisfactorily with intensive behavioral treatment alone, the other 1/4 requiring supplemental medication (MTA Cooperative Group, 1999).

Other treatments have varying degrees of documentation (Arnold, 1999). Most are not likely to be effective for the majority of patients with ADHD. Elimination diets (few-foods diets or oligoantigenic diets) have convincing controlled studies, either placebo-controlled challenges or sham comparison diets, with a moderate effect. However, sample selection leaves it unclear as to what proportion of ADHD would be helped substantially by such a diet. Clearly it would be considerably less than half, possibly as low as 5 %, a guesstimate that is widely quoted but may be too low. Thyroid treatment is effective for the 2-5% of ADHD who have a thyroid abnormality, but not for others. Similarly, deleading is effective only for those with elevated lead levels, a small proportion. Electroencephalographic biofeedback has some promising pilot data, but lacks a sham-controlled study and it is not clear what proportion of ADHD would benefit if it proves effective. Obviously, nutritional supplements would be effective only for those with a deficiency (absolute or relative) of the nutrient in question.

Up to this point, the few clinical trials on nutrient treatments, such as megadose multivitamins, amino acids, and essential fatty acids, for ADHD have yielded disappointing results (Arnold, 1999). They must be considered experimental treatments at this time for the majority of patients with ADHD, though some have shown more promising results in other disorders. I hope they may be found, after appropriate studies, to have some future utility for selected ADHD patients with specific metabolic profiles, but this is a hope, not a basis for current therapeutics.

Treatment selection should consider individual patient characteristics and preferences (MTA Cooperative Group, 1999b; Arnold, 1999; Jensen et al, 2001). For example, ADHD patients with a treatable cause (thyroid abnormality, food sensitivity, heavy metal poisoning) should have the cause treated, as the first priority. ADHD patients with comorbid conduct disorder or oppositional-defiant disorder generally need medication. Those with comorbid anxiety disorder can usually benefit from either behavioral treatment or medication. Those with both comorbidities often need both kinds of treatment. Those with comorbid mood disorder may benefit from an antidepressant or a combination of antidepressant and stimulant. Treatment ideally should be selected by a cooperative effort of patient, parent, and clinician (physician, psychologist, or other trained health professional with experience in diagnosing and treating ADHD), who informs and guides the patient and family.

IV. ADHD CLAIMS

A. Evidence Needed to Substantiate Effectiveness in Treating ADHD

Convincing evidence that a new or previously unproven treatment is effective for ADHD should flow from at least one study with the following features. While an acceptable study might compromise one or another of these standards, any such deviations from the ideal diminish its value in the proportion to which it deviates. Absence of certain features would constitute a fatal flaw. The ideal features of a supporting study include the following:

1. A sample of rigorously diagnosed patients with ADHD. (Animal or metabolic studies are not sufficient, and the sample should not be just consecutive referrals for learning or behavior problems.)

2. A clear rationale and design meeting accepted scientific standards for a randomized clinical trial, such as the following:

3. Careful attention to inclusion and exclusion criteria, considering the population the results are to be generalized to and possible subject characteristics that might interact with the treatment. For example, the age of the sample (prepubertal vs. adolescent or adult) may be important if it turns out that puberty affects the action of the treatment. If a wide age range is included, then one should allow sufficiently large numbers in each age category for enough power to examine the results separately if necessary.

4. Careful attention to both dimensional and categorical aspects of diagnosis, including normed rating scales and structured diagnostic interview, as well as review by child psychiatrist or other expert in ADHD diagnosis.

5. Detailed characterization of subjects prior to entry: comorbidity, age, socioeconomic status, race, intelligence, medical/neurological problems.

6. Carefully thought out plan for dealing with other treatments: either excluding them with an appropriate washout period, or keeping them consistent throughout the trial, or monitoring them as an outcome measure.

7. Power analysis to determine the minimum sample size, based on the smallest effect size that must be detected. For example, to have an 80% chance of detecting a moderate effect (Cohen's *d* of 0.5) at a significance level of $p<0.05$ would require a sample size of 64 assigned to each condition (placebo and active treatment). To have an 80% chance of detecting a small effect (Cohen's *d* of 0.25) at a significance level of $p<0.05$ would require a sample size of 252 assigned to each condition (placebo and active treatment). Larger samples could detect smaller effects, but in general, effect sizes smaller than 0.2-0.3 are not considered worth detecting –i.e., if a treatment cannot make at least that much difference, it is not considered a loss to miss the effect. For comparison purposes, stimulant medication

usually shows a placebo-controlled effect size of 0.9 to 1.3, requiring samples of 10-20 in each condition for statistical significance.

8. Randomly assigned double-blind placebo condition for any treatment involving ingestion of pills, tablets, capsules, elixir, etc. This is necessary to control for history, maturation, statistical regression to the mean, and the well-known placebo effect, the improvement that arises from positive expectation and the healing power of nature and time. Most neuropsychiatric disorders, including ADHD, are subject to considerable placebo effect. Randomly assigned placebo patients also control for the effect of history (unusual events, stresses, or relief from stress) and developmental maturation (the fact that as children age, they tend to get more attentive, calmer, and less impulsive). The placebo must be matched to the tested product in appearance, taste, and any other identifying characteristics. The quantity used must be the same as is used in the active treatment, and the monitoring must be the same. The assignment to placebo or active treatment must be by chance, such as flipping a coin or using random numbers, and should generally be done by someone who did not evaluate the patients (e.g., collaborating pharmacist or data center). An added refinement not usually done would be to match the subjects in pairs by characteristics believed important (e.g., age, IQ, sex) and then randomly assigning one of each pair to each condition.

9. Testing of actual product. The active treatment tested should be what is actually to be used once marketed, in terms of dose, active components, inert binders, colors, etc. Testing of separate ingredients can be misleading. The combination of ingredients may interact in some unexpected way, perhaps by affecting absorption or metabolism. Further, the interaction could be either toxic, neutralizing, or synergistic. (An argument might be made for demonstration of effect of separate ingredients on the disorder in question, coupled with some demonstration that the ingredients do not interact other than to add their effects. However, such an approach would be at least as expensive as the straightforward testing of the actual product in the first place, and not as satisfactory.)

10. A well-considered a priori main outcome measure (or measures) that is widely accepted, easily understood, and clinically meaningful. In general, it is best to keep the number of measures to a minimum to avoid experiment-wise error and the need for Bonferroni correction. E.g., if there are 20 outcome measures, 1 of them is expected by chance to be "significant" at the 0.05 level of probability, thus producing a false positive. On the other hand, since ADHD is by definition a disorder manifested in more than one setting, multiple informants are desirable. There are several ways to composite information from different informants. One common one is for the clinician or other investigator to obtain information from patient, parent, and teacher and integrate them into a "clinical global impression"(CGI). Another is to have all informants fill out the same scale or set of scales and then average them to obtain a composite outcome measure. Another acceptable approach is to use 2 or 3 outcome measures, one from parent, one from teacher, and perhaps one from clinician.

11. Clinically meaningful duration of treatment and follow-up. The appropriate duration of the

treatment trial is partly determined by how fast the treatment is expected to work. The formal comparison should be long enough to insure the treatment has been given a fair chance to work and that there is time for placebo effect to stabilize or dissipate. For nutritional treatments, there must be time for metabolism to re-stabilize. For example, amino acid trials showed some short-term effect the first week or two which dissipated by 2-3 months as the liver enzymes up-regulated to "detoxify" the increased amount of amino acids. For a parallel-group study, a longer post-treatment follow-up is desirable to check lasting effects.

12. Systematic collection of safety and side effect data. Side effects and other "adverse events" should be recorded and compared between the active treatment and placebo.

13. Credible investigators. The investigative team should include experts in clinical trial design and implementation, a statistical consultant, and clinicians expert in the treatment being tested. The study should be designed and implemented by experienced, appropriately credentialed investigators who are not unduly influenced by financial ties to the product –arm's length testing. This could be accomplished through a grant to a university investigator to carry out appropriate studies (grant not to depend on results of the study) or by hiring an independent clinical research organization.

14. Randomized clinical trial statistical methodology, including use of intention-to-treat analysis as the primary analysis (not just analysis of "completers"). The reason for intent-to-treat analysis is that subject attrition is usually biased. E.g., if one treatment is very effective with no side effects and the other is completely ineffective, the first group will have little or no attrition because the subjects are happy with the results, but the other treatment may have 50% attrition, selective for those who are doing poorly, with only the better-faring cases (placebo responders and less serious cases) left as "completers". This attrition bias makes the second treatment look better than it really is if only the completers are analyzed. Thus the truest comparison of the randomly assigned groups is to include all who were assigned to each group, using their last available assessment (last observation carried forward). Alternatively, the comparative dropout rate itself can legitimately be used as an outcome measure (survival curve analysis). The corollary is that sample size should not anticipate dropouts (other than as introducing noise into the data); rather, sufficient effort should be devoted to obtaining a firm commitment from subjects prior to entry and maintaining their cooperation once entered.

15. The final report should pass peer review for a reputable journal, and should include the rationale, hypothesis, details of methodology as highlighted above, sample characterization and attrition, full descriptive statistics, and results of statistical tests, including enough information to calculate standardized effect sizes.

16. Clinical and statistical significance. The product must, of course, have an effect that is statistically significant. In addition, the clinical significance should be enough to justify the risk, expense, and nuisance. Effectiveness is often measured by standardized effect size

(ES), Cohen's *d*, which is the difference from placebo divided by the standard deviation of the placebo –in other words, the number of standard deviations by which the treatment is better than placebo. The risk assessment should consider not only possible toxicity or side effects of the product, but also the possibility that it might replace a more effective treatment if the patient cannot afford both or if the two treatments are not compatible. A treatment that is extremely safe, very cheap, easy, and can be combined with other effective treatments might be worth using even if it has only a small effect size (e.g., 0.2). A treatment with considerable continuing expense (e.g., in the range of prescription medication) or moderate risk should have a moderate or larger ES (about 0.5 or greater) to justify its use. With a combination of risk and expense, an even larger ES would be needed.

One well-controlled, rigorous, randomized clinical trial as described above showing definite statistical and clinical benefit would be acceptable to substantiate effectiveness and safety, but it is customary to replicate such results before considering a treatment established. There are several reasons for this, both statistical and clinical. For practical reasons, studies are designed with built-in acceptance of the 5% possibility of a false positive. Further, most studies, even good ones, have some flaws, minor deviations from the ideal standards described above. E.g., peculiarities of sample recruitment and screening may skew the results at a given center, or a given investigator may unwittingly be seeing through the blind. There might even be population differences at a given site, especially for nutrition. For such reasons, replication of the results by a different investigator at a different site supports the validity of the effect and makes a more convincing case.

When multiple studies are done, there may be some with significant results and others without. Study design usually accepts a 5% possibility of false positive and a 20% possibility of a false negative, making a negative study four times as likely to be false as a positive study. Therefore a positive study generally carries more scientific weight than a negative one if both are rigorously designed and executed with adequate controls. However, each study must be evaluated on its own merits: a poorly designed or poorly executed positive study would be outweighed by a well-controlled negative study. Open trials are almost always outweighed by placebo-controlled trials. Negative studies (those that fail to find statistically significant results) tend not to be published unless they are exceptionally well done, with adequate guards against Type II error (false negative). On the other hand, positive studies may be published even if flawed, on the premise that they will inspire better controlled replication. This publication bias tends to neutralize the statistical expectation of four times as many false negatives as false positives from well-designed studies. In evaluating study reports, the details of method are important. For negative studies, one must ascertain whether the sample was sufficiently large to have the power to detect the expected effect, and whether the dose was optimal (and, unfortunately, whether the investigators may have started out with a prejudice against the treatment that could have resulted in merely cavalier attempts to find the effect). For positive studies, the critical issues are the blinding procedures, sample selection, relevance of assessments, statistical method, and objectivity of investigators. The principles of study critique described over the last 4 pages are generally accepted by clinical trials experts.

For acceptance into common use, "alternative" treatments (nonpharmacologic, non-

behavioral) should meet roughly the same standard of clinical-scientific evidence as do medications and behavioral treatments. We are not talking here about the stringent requirements for FDA approval, but the reasonable scientific evidence that a good clinician should require to adopt any treatment. Any treatment should pass efficacy and safety muster on the basis of recognized clinical and scientific principles of evidence as outlined above.

B. Claim that Pedi-Active A.D.D. Treats or Mitigates ADHD or its Symptoms

The claim that Pedi-Active A.D.D. treats or mitigates ADHD or its symptoms appears unsubstantiated, based on these considerations:

No study of this product (this combination of ingredients) for ADHD or its symptoms has been submitted or found.

The company apparently tries to argue that the ingredients are separately effective, but submits no evidence that they are additively effective or even that they do not have some harmful interaction, and the evidence for the individual ingredients is at best flawed and strained. Most of the reports submitted fail the tests for an acceptable clinical trial on several counts. The following will examine in more detail the evidence available regarding the effect on ADHD of the separate ingredients. The two main components of Pedi-Active A.D.D. seem to be 1) dimethylaminoethanol (DMAE) and 2) Leci-PS, which apparently contains the rest of the list of ingredients in Table 1. These two main components will be separately discussed.

1. DMAE Evidence

Consulting Table 2, we note that most of the references used the acetamidobenzoate salt, previously marketed as Deaner (generic name deanol). One of the references to a tartrate salt (Murphree) implied that it might not be as good as the lactate salt, but there does not appear to be a basis for saying whether the salt makes a difference or not. The salt used in Pedi-Active A.D.D. is bitartrate This might be an issue worth exploring further if the references were not so flawed in other ways to an extent that makes the salt issue academic:

Most of the references did not use samples of well-diagnosed children with the disorder in question to allow generalization to treatment of ADHD. Many had heterogeneous samples, some with epileptic or other neurologically disordered patients mixed in (Oettinger, Kugel & Alexander, Pfeiffer), samples defined by mental retardation (Fleming & Orlando, 1962; Jacobs, 1965), reading retardation (Huddleston et al., 1961), globally conceived behavior problems (Geller, Conners 1973; Bostock & Shackelton, 1962), mixed learning disorder and behavior problems (Lewis & Young, Oettinger report analyzed by Conners), "diagnoses" made by teacher referral (Coleman et al, 1976), mere descriptive characterization as hyperactive or hyperkinetic (Lewis & Lewis), no diagnostic description (Duncan, DiMascio & Finnerty), or even normal adults (Murphree). Another problem common to many of the reports is lack of sufficient detail to fully evaluate what was done in the study.

Some of the reported studies did not include a placebo control (Oettinger J. Peds & 1977; Pfeiffer, 1957; Bostock & Shackleton, 1962).

Several studies reported results that were not significant or were of questionable significance and/or nil to questionable clinical significance. Lewis & Lewis found most measures to have no significant effect, and the placebo-controlled ES was less than 0.2, suggesting lack of clinical significance even if the statistical test had been significant. DiMascio & Finnerty's study, which apparently was published as Coleman et al, found a barely significant clinician rating, but practically no effect on several other measures (including teacher ratings), suggesting the blind was not effective; in any event the ES was small, and this should be counted as an essentially negative study, especially after appropriate Bonferroni correction, which was not done in the report. Geller had no significance test, depending on impressionistic interpretation of results. Kugel and Alexander found no significant difference between DMAE and the placebo. The Duncan LSU study analyzed by Conners found 58% of deanol and only 10% of placebo improved by clinician rating, but no difference on parent or teacher ratings, generally accepted as the gold standard in ADHD research; again, the positive results on clinician rating but not other measures suggests possible leaks in the blinding procedure; in any event this study on balance must be classified as negative or at most suggestive, with its negative parent and teacher ratings. Fleming & Alexander found no improvement in reaction time or attention. Jacobs found nil to negligible effects on ratings of attention, alertness, and tantrums. The articles by Re, by Conners (1973), by Saccar, and by Millichap were review articles and only as valid as the studies on which they were based.

Some of the studies used higher doses than currently or previously recommended by the distributor of Pedi-Active A.D.D. Lewis and Young titrated within 2 weeks to 500 mg a day, considerably above the 300-400 mg in the current daily recommendation of 4-8 tablets of Pedi-Active A.D.D., and significantly (5 times) above the 50-100 mg in the previous recommendation of 1-2 tablets a day. Lewis and Lewis also used 500 mg/day, well above the previous and current recommendations for Pedi-Active A.D.D. DiMascio & Finnerty (Coleman et al) also titrated to 500 mg/day. Re, in a review article, recommended 500-1000 mg/day. Millichap recommended 10-1000 mg/day individually titrated.

Thus essentially all of the studies submitted regarding DMAE for ADHD can be disqualified on the basis of lacking one or more of the features of a convincing, relevant clinical trial, and some actually suggest no to negligible effect. A few are good enough, however to consider as pilot data. In particular, Lewis and Young seems the most promising study. It included both placebo and active comparator control (methylphenidate, an accepted standard of current treatment). Though the sample was poorly defined and diagnosed, it probably contained a good proportion of children with ADHD, being selected for inappropriately poor school performance, "many with hyperactivity". Both DMAE and methylphenidate (MPH) were significantly better than placebo on several tests, including behavior ratings, and were not significantly different from each other. However, in actual effect, DMAE fell midway between placebo and MPH. E.g., the behavior scale improvement was 4 for placebo, 10 for DMAE, and 17 for MPH, with the raw scores at end of treatment being 27 for placebo, 26.3 for DMAE, and 16.9 for MPH (lower score better). IQ scores at end of treatment, all starting at 100.5-100.8, were placebo 103, DMAE 110, MPH 115. DMAE

shows a placebo-controlled ES of about 0.5, medium, on parent ratings. Across the battery of tests, DMAE showed placebo-controlled ES's of 0.1 to 0.6 (minimal to medium), compared to 0.8 to 1.3 (large) for MPH. These constitute rather promising pilot data, which would warrant a well-controlled study following the guidelines outlined above to test whether Pedi-Active A.D.D. might have a small to medium effect, which might be useful for mild cases. They do **not** constitute adequate substantiation for treatment of ADHD with the dose of DMAE in the currently recommended dose of Pedi-Active ADD, let alone the previously recommended lower dose, because: the sample was not adequately diagnosed/screened; the dose used was considerably larger than the current Pedi-Active ADD recommendation and 5 times the previous recommendation; and intent-to-treat analysis was not done. Another promising study was Oettinger's placebo-controlled trial analyzed by Conners (1971). It showed a weak suggestion of effect, with most tests nonsignificant, but teacher ratings and continous performance test omissions significant at $p<0.05$ without Bonferroni correction for multiple testing.

Such promising studies (Lewis & Young; Oettinger, 1971) must be balanced against the discouraging results in some other studies. Perhaps the latter were underpowered (too small a sample) or underdosed, yielding false negative results; conversely it is conceivable that the positive results in a few studies resulted from chance (false positives). Overall consideration of all the submitted studies suggests that if the proper randomized clinical trial is done, it will probably find a significant small-to-moderate ES (0.2 to 0.5) for DMAE in treatment of ADHD, but at doses higher than those contained in the recommended dose of Pedi-Active A.D.D. The probability that such a result can be found does not constitute current substantiation of the Pedi-Active ADD claims; it merely recognizes the promising nature of the pilot data for DMAE, though at doses higher than found in the recommended doses of Pedi-Active ADD..

2. **Evidence for Leci-PS**

The submitted "evidence" for Leci-PS, which contains the phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine (and presumably the list of fatty acids in Table 1) is more diffuse, confusing, and contradictory than for DMAE, almost a "wild card" approach (like redefining a deuce as an ace in an attempt to fill out a winning hand). Many of the references concern efficacy of such nutrients for senile dementia, a point not in dispute, or the need for omega-3 fatty acids for normal development of brain and retina, also not in dispute, or the need for longer-chain polyunsaturated fatty acids (such as docosohexaenoic acid), which are not listed as ingredients of Pedi-Active A.D.D. Before examining the 4 relevant references, I will try to clarify some of the issues about essential fatty acid supplementation, which the submitted materials suggest the company does not seem to understand. Most of the clarification below can be found in Horrocks & Yeo (1999), Arnold et al (1999), and standard updated biochemistry textbooks as well as in some of the materials submitted..

Essential fatty acids (EFAs) are so called because they are essential to good health but cannot be manufactured *de novo* by the human body's metabolism. In this sense they are like vitamins and essential amino acids (the protein building blocks of the body). True, the body can make fat (fatty acids) out of carbohydrate and protein, but not the two series of *essential* fatty acids,

which can only be made by plants, not animals. These two series have the first unsaturated double bond 3 carbons from the noncarboxyl (non-acid) "tail" of the chain and 6 carbons from the tail, respectively. They are respectively named omega-3 or n-3, and omega-6 or n-6 series of EFA. (Omega, the last letter of the Greek alphabet, indicates the end, the last carbon in the tail, and the "n" indicates the number of carbon atoms in the chain). The two nomenclatures (omega or n) are interchangeable, the important distinction being whether it's -3 or -6. Each series (-3 or -6) has many fatty acids of varying lengths and numbers of additional unsaturated double bonds. EFAs are sometimes called polyunsaturated fatty acids (PUFAs), of which they are a subset; EFA is the more specific term because theoretically there can also be PUFAs (n-7, n-9) that are not essential (they can be manufactured by the body).

The body can to some extent convert the shorter EFAs into the longer EFAs within each series, but must have a beginning substrate with the first unsaturated bond at 3 or 6 carbons from the tail, respectively, and cannot convert an n-6 EFA to an n-3 acid., and probably not vice versa. The short dietary progenitor for the n-3 series is alpha-linolenic acid, or just plain linolenic acid, with 18 carbons and 3 unsaturated double bonds; the longest in the n-3 series is docosahexaenoic acid (DHA), abundant in fish oil, with 22 carbons and 6 unsaturated double bonds. For the n-6 series, the short dietary progenitor is linoleic acid, with 18 carbons and 2 unsaturated double bonds; ordinarily the longest in the n-6 series is arachidonic acid, with 20 carbons and 4 double bonds, although a 22-carbon n-6 acid with 5 double bonds is also made, especially as a substitute for DHA if there is a shortage of n-3 EFAs. The two series (as well as other series, of nonessential fatty acids) compete with each other for the critical desaturase enzymes needed for building the longer EFAs from the shorter. There is some suspicion that the evolved human desaturases, especially delta-6-desaturase (the first step), are not satisfactorily efficient for building all needed longer-chain EFAs from shorter dietary sources. If so, then for the optimal amount of the longer EFAs, some must be ingested directly, especially for infants and young children, whose brains are rapidly myelinating, with consequent need for long-chain EFAs, which are incorporated into neuronal membranes as phospholipids (such as phosphatidylcholine or phosphatidyl serine). Indeed, human milk contains much larger amounts of DHA than cow's milk, and supplementation of formula with DHA in a controlled bottle-feeding study produced smarter toddlers than unsupplemented formula.

One of the intermediate EFAs in the n-6 series is gamma-linolenic acid, not to be confused with alpha-linolenic acid (plain linolenic acid) of the n-3 series. These are completely different, and one cannot be converted to the other. They have a similar name because they both have 18 carbons and 3 unsaturated double bonds, but the location of the first double bond, 6 or 3 carbons from the tail, makes a profound difference in the biochemical activity and metabolic and neurostructural role.

The inefficiency of human desaturation and the relative scarcity of n-3 EFAs in modern diets have inspired a number of studies of supplementation for various disorders, with results ranging from gratifying to discouraging. It now appears well-established that supplementation with the n-3 series is beneficial in preventing cardiovascular disease. The value of DHA supplementation in infant formula appears established. Fish oil, high in DHA, has been shown in a placebo-controlled pilot study to benefit bipolar mood disorder (Stoll, 1999). Phosphatidylserine and phosphatidylcholine, presumably including some of the longer-chain EFAs, seem useful in senile

dementia, both ameliorating Alzheimer's symptoms and preventing to some extent the ravages of aging. Thus it is understandable that many investigators had high hopes for EFA supplementation in ADHD. Unfortunately, the results here have been more discouraging.

Studies comparing blood EFA profiles of children with ADHD to normal controls do indicate differences suggesting possible deficiencies in ADHD (Mitchell et al, 1984; Stevens et al, 1996). However, actual clinical trials using EFA supplementation as treatment for ADHD have shown at best equivocal results, whether for n-6 (Aman et al, 1987; Arnold et al, 1989) or n=3 (Stevens-Burgess Purdue group, in review; Voight, unpublished). The Arnold 1989 reference is an interesting case study of the confusion and mis-citation reigning in the submitted-materials strategy: This reference is cited in support of Pedi-Active A.D.D., with the comment "The essential fatty acid, linolenic acid, described in this study is the same as that of our product." The dose of linolenic acid listed in table 1 for the currently recommended dose of Pedi-Active A.D.D. is 18-24 mg; but the dose of *gamma*-linolenic acid used in the Arnold study was 320 mg., and the authors suggested that this dose may be too low for some patients. The article ends with the statement, "...gamma-linolenic acid supplementation should be considered an experimental treatment for ADHD. The data reported here do not establish its effectiveness." Thus even if the dosage and type of EFA had matched, the cited article actually calls into question the claims for this supplement rather than supporting them.

Let us now return to the 4 articles directly relevant to Leci-PS in ADHD, summarized in Table 3. Unfortunately, many details are missing in the synopses provided, but some comments can be made. It seems clear that none of the studies would qualify as acceptable substantiation of claims for ADHD. Two of the studies used the actual ingredient Leci-PS, and the other two (by Gant) used soy phospholipids roughly comparable to Leci-PS, though apparently not enriched with PS, and in one case also supplemented with fatty acids and other individually targeted supplements. The doses used, when stated, appear larger than those contained in the currently recommended daily Pedi-Active A.D.D. dose of 4-8 tablets, and significantly greater than in the previously recommended 1-2 tablets per day. For example, the Kunin study used 200 mg/day of phosphatidylserine and the Ryser study used 100-300 mg/day, compared to 120-160 mg in 6-8 tablets of Pedi-Active A.D.D. and 20-40 mg in 1-2 tablets. The second Gant study used 1-3 grams of phospholipid compared to about 0.5 gram total lipid in 8 tablets of Pedi-Active A.D.D.. Three of the studies, including both with Leci-PS, are uncontrolled open trials (no placebo or comparison treatment) and highly subjective in the assessment of outcome. The results, though optimistic, verge on testimonial rather than data. No dimensional data are provided. Two of the studies wander out of the appropriate age range, either into toddlerhood or into adolescence.

The first Gant study is a cut above the other 3, and provides some promising pilot data. Though no placebo was used, there was a comparison group receiving methylphenidate, an established treatment for ADHD. The phospholipid used was mainly phosphatidylcholine, not the same as Leci-PS, which is enriched in phosphatidylserine. Both groups improved from pre-treatment to post-treatment on 5 of 11 Continuous Performance Test scales, a Conners behavior scale, and "scholastic performance," which is not defined or measured in the report. The implication is that there was no significant difference between the two treatments. It is not clear

how blinded the assignment and treatment were, but that may be irrelevant if the clinician and parents believed that both treatments were effective. Without a placebo control, and without knowing the dose and titration method for the methylphenidate, it is difficult to interpret the similarity of outcome for the two treatments. The improvement could all be placebo effect. Or the methylphenidate could have been poorly managed: the MTA study (MTA Cooperative Group, 1999a) demonstrated that carefully managed intense methylphenidate treatment yields significantly better results than the way the same drug is routinely managed in the community. Or there could be a clinically significant difference between the treatments that was not picked up by the low power of the small sample. With only 10 subjects in each group, the difference between treatments would have to be very large (ES over 1.0) to have an 80% chance of detecting it. Thus while this study provides some provocative pilot data, it does not substantiate a claim for Leci-PS in ADHD.

3. **Conclusion:**

Examination and review of the available materials do not reveal adequate substantiation for an effect on ADHD or its symptoms by either Pedi-Active A.D.D. or its separate ingredients, especially not at the doses recommended by the distributor. No trials at all with Pedi-Active A.D.D. were reported. For the ingredients, there are promising pilot data at higher doses, especially for DMAE, but no convincing positive report of a well-controlled clinical trial using the doses in the recommended daily amount of Pedi-Active A.D.D. If such a trial is done, it is likely to detect an effect considerably weaker than standard treatment, if at all.

This opinion is at variance with that expressed by Charles Gant in a December, 1998 unpublished summary. In that summary, in addition to citing basic-science findings that are not at issue, he cites some of the same material examined above and concludes in regard to ADHD/ADD "I would find it hard to imagine a clinical scenario in which phospholipids such as phosphatidylserine or precursors such as DMAE would not be beneficial...Certainly the outcomes of studies using these nutritional supplements would seem to support such a conclusion." Such a conclusion is only as valid as the data on which it is based. The difference between Dr. Gant's opinion and mine is his uncritical acceptance of flawed studies, some even without a placebo control, as if they satisfied acceptable criteria for a randomized clinical trial. In this regard, it is noteworthy that he also cites the Arnold 1989 reference in support of a statement that EFAs "have been successfully used for some time to treat ADD/ADHD." Recall that that article ends with the statement "The data reported here do not establish its effectiveness." His incomplete grasp of the relevant information is also illustrated by the statement "...ADD and ADHD are associated with a multiplicity of possible causes, *all of which* [emphasis added] are relevant to potential imbalances or deficiencies of lipid and phospholipid metabolism." Such a sweeping statement has little if any foundation in the literature, ignores possible causes with just as good evidence that are not obviously related to lipid metabolism, and would not be accepted by the vast majority of experts on ADD/ADHD.

V. OTHER CLAIMS (NOT SPECIFICALLY ADHD AND ITS SYMPTOMS)

A. **Claim that Pedi-Active A.D.D. will improve the attention span of children who**

have difficulty focusing on school work.

This and the following claim have a slightly lighter burden of substantiation than the claims related to ADHD/ADD, in that it is not necessary to have a well-diagnosed sample of ADHD for a supporting study. However, the other requirements for a randomized clinical trial should be met, such as double-blind randomized placebo condition, clearly articulated method, appropriate dose range as found in the product recommendations, appropriate measures relevant to the claim, sound statistical analytic strategy, and both statistical and clinical significance. Further, even though the sample does not have to have well-diagnosed ADHD, it does need to be of the appropriate age and be documented to have difficulty focusing on school work. These requirements would be generally agreed on by most experts on attention and clinical trials.

Although short attention span is one of the cardinal symptoms of ADHD, this claim does not specify ADHD/ADD so its substantiation does not require that the sample be well-diagnosed with the disorder. Studies with a nondescript sample might suffice if they meet the other requirements for an adequate clinical trial. Unfortunately, none of the studies available do meet the other requirements; so the critique given for the ADHD/ADD claim generally applies also here.

Several of the studies do have placebo control and report of attentional function, and these are worth noting. The Duncan LSU study reviewed by Conners included continuous performance test (CPT) data, a measure of attention, and this showed a barely significant ($p=0.05$) benefit for Deaner (DMAE. deanol) compared to placebo, but Conners questioned the validity of this finding because only 3 statistical tests out of about 2 dozen in this study were significant, and one would expect almost this many by chance: by definition, one out of every 20 statistical tests will be significant at 0.05 by chance. Further, Conners questioned the effectiveness of the blind in this study. The Oettinger study analyzed by Conners showed a significant deanol effect ($p=0.049$) for CPT omissions, but again this was one of only two significant findings in about 2 dozen statistical tests, and one would expect one out of 20 statistical tests to be significant at 0.05 by chance. The Geller study reported better puzzle performance for the Deaner group, but with no test of significance. The DiMascio & Finnerty study found no Deaner difference from placebo in teacher attention ratings. Two studies in samples with mental retardation reported on attention measures: Fleming & Orlando found no improvement in attention or reaction time; Jacobs found a negligible effect, and it is not clear how well one can extrapolate from a sample with MR. Thus the evidence for improvement of attention (disregarding diagnosis) by DMAE (Deaner, deanol), though perhaps a shade better than for diagnosed ADHD, is equivocal and erratic. There may be a small effect, but the available studies do not adequately demonstrate it, and we cannot say that this claim is substantiated. Of course, there are not even any studies, let alone findings, examining this claim for the marketed combination product. Conclusion: the claim is not substantiated.

B. **Claim that Pedi-Active A.D.D. will improve scholastic performance of children who have difficulty focusing on school work.**

This, like the preceding claim, has a slightly lighter burden of substantiation than the claims related to ADHD/ADD, in that it is not necessary to have a well-diagnosed sample of ADHD for a

supporting study. However, the other requirements for a randomized clinical trial should be met, such as double-blind randomized placebo condition, clearly articulated method, appropriate dose range as found in the product recommendations, appropriate measures relevant to the claim, sound statistical analytic strategy, and both statistical and clinical significance. Further, even though the sample does not have to have well-diagnosed ADHD, it does need to be of the appropriate age and be documented to have difficulty focusing on school work. These requirements would be generally agreed on by most experts on clinical trials.

Scholastic performance broadly conceived could include achievement (as shown on standardized tests) as well as academic performance (grades, work completion and quality, good exam scores). Thus this claim can refer to achievement, academic performance, or both. The available placebo-controlled reports are remarkably devoid of solid data in either regard. Several reports mention school improvement but offer no data to back up the impression. Only two reports included measures of achievement/performance. Huddleston et al (1961) found no significant effect on reading achievement, but did find an effect on clerical speed and accuracy in an aptitude test, which they thought might eventually aid reading. That sample was selected for reading delay, not for difficulty focusing on school work In the other study with achievement testing (DiMascio & Finnerty or Coleman et al), the placebo group showed significant improvement in reading and arithmetic achievement on standardized tests while the Deaner (DMAE) group did not, and spelling was not significant. In short, the data available go against this claim rather than supporting it. No placebo-controlled study included such measures of academic performance as a timed arithmetic test. And, of course, there was no study of academic performance or achievement using the combination product as marketed. Most experts would agree that this claim is not substantiated.

C. **Claim that Pedi-Active A.D.D. will improve the attention span of children who suffer from ADHD/ADD.**

Since short attention span is one of the symptoms of ADHD, this claim is not essentially different from the claim that Pedi-Active A.D.D. will mitigate ADHD and/or its symptoms. Everything that was extensively described for that claim and its substantiation applies here, with the same conclusions.

In addition, the placebo-controlled evidence specific for DMAE attentional benefit was reviewed in regard to the claim of improved attention span without a diagnosis of ADHD/ADD. The conclusion was that the claim of improved attention span was not substantiated even when the diagnostic issues were ignored. Clearly, if we add the requirement that the sample have well-diagnosed ADHD/ADD, then the lack of substantiation is even more obvious. Thus the claim is not substantiated for the separate ingredients, let alone for the combination as marketed. Other ADHD experts familiar with evidence-based treatment and/or clinical trials methodology will agree that this claim is not substantiated.

D. **Claim that Pedi-Active A.D.D. will improve the scholastic performance of children who suffer from ADHD/ADD**

Scholastic performance broadly conceived could include achievement (as shown on standardized tests) as well as academic performance (grades, work completion and quality, good exam scores). Though impaired scholastic performance is not one of the 18 symptoms of ADHD/ADD in Table 4, it is a frequent associated problem and often supports the impairment criterion for diagnosis.

Substantiation for this claim would need to meet the criteria explained under the claim for mitigation of ADHD and its symptoms, and in addition would need to have evidence specifically relevant to scholastic performance. The latter issue was reviewed under the claim for improved academic performance regardless of diagnosis. Only two placebo-controlled studies were found with data directly measuring some aspect of scholastic performance. One (Huddleston et al, 1961) found no significant effect on reading in a sample selected for reading delay rather than ADHD/ADD. The other (Di Mascio & Finnerty) found significantly improved reading and arithmetic for the placebo group but not for the Deaner (DMAE) group. Thus the placebo-controlled data available run counter to the claim, far from supporting it. Other experts on ADHD and evidence-based treatment would agree that this claim is not substantiated.

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SUMMARY OF RESPONDENTS' EXPERT REPORTS

Expert	reviewed DMEA data/theory	reviewed other ingred. data/theory	reports on patient observations	opines on nature of ADHD
Breggin, Peter R. (psychiatry, MD)	Lewis & Young "evidence in literature" Oettinger, Coleman, DiMasco & Finnerty, Fields, Geller, Lewis & Lewis [see 24 docts recd from counsel][1]	--	observations in own practice	nature & symptoms of ADHD
Cott, Jerry, PhD (pharmacology)	Lewis & Young Kiss & Crilly, Lohr & Acara, Alvaro, Miya-zaki, Ansell & Spanner, Dainous& Kanfer, FDA proceeding, Oettinger, Millichap & Fowler, Dimpfel, Nagy & Floyd, Groth	use of PS in Europe Mitchell, Stevens, Burgess, Ryser Pelligrini [see 44 docts. in Appendix re: DMAE, PS]	review of Kidd patient study	nature & symptoms of ADHD

[1] In each case, the vast majority of documents that Respondent ' counsel sent to the experts were scientific articles relating to the largest ingredients in PediActive A.D.D. – DMAE (2-dimethylamino-e hanol), Phosphatidylserine (PS), or Phosphatidylcholine (PC).

Expert	reviewed DMEA data/theory	reviewed other ingred. data/theory	reports on patient observations	opines on nature of ADHD
Crook, William G. (MD pediatrics)	Riker, Pfeiffer, Crook Oettinger [see 14 docts from counsel]	Kidd study [recd 14 pubs. from counsel]	review of Kidd patient study, effect of diet on own patients	nature & symptoms of ADHD
Galland, Leopold (MD)	"familiar with much of existing data" + [see 14 docts from counsel]	"familiar with much of existing data" + [see 14 docts from counsel]	observations in own practice	nature & symptoms of ADHD
Gant, Charles (MD)	[see 35 docts from counsel]	"many studies"re: PS [see 35 docts from counsel]	in-office study observations from own practice	nature & symptoms of ADHD
Hallowell, Edward (MD psychiatry)	[reviewed 31 docts from counsel]	[reviewed 31 docts provided by counsel]	observations in own practice	nature & symptoms of ADHD

Expert	reviewed DMEA data/theory	reviewed other ingred. data/theory	reports on patient observations	opines on nature of ADHD
Kidd, Paris M. (Phd biol/zoolog)	online data bases, primary sources, [cites 22 references]	18 clinical trials & hundreds public's re: PS and brain function [cites 22 ref-references]	own 2 studies with Kunin & Ryser on patients	--
Kunin, Richard (MD psychiatry)	Lewis & Young,[2] own study with Pfeiffer [no attchmt re: counsel submissions]	own study	observations from own practice	nature & symptoms of ADHD

[2] Refers to "double-blind placebo-controlled study," most likely Lewis & Young.

Expert	reviewed DMEA data/theory	reviewed other ingred. data/theory	reports on patient observations	opines on nature of ADHD
Packer, Lester (PhD biochem)	gen'l knowledge of nutritional chem., Du Vigneaud, Dorman, Levron & Le Fur, J. Pharmacol Ther. Nagy & Floyd Arch Gerontol Geriat., Dolganiuc et al Arch Microbiol. Imm, 2 Packer bks [recd 47 docts from counsel]	gen'l knowledge of nutritional chem., recent studies, Crook [recd 47 pubs from counsel]	--	--
Re, Osvaldo Norberto (MD)	Lewis & Young, Riker studies, Vigneaud/Crowder, Pfeiffer, Groth, Mahler & Coredes, Danysz, Haubrich, Silbergeld & Goldberg, Jenden, FDA [cites 19 references]	--	observations of own patients	nature and symptoms of ADHD

Expert	reviewed DMEA data/theory	reviewed other ingred. data/theory	reports on patient observations	opines on nature of ADHD
Sanford, Joseph (Phd)	Lewis & Young, Muphree, Coleman Coleman, others [recd 33 docts from counsel]	--	--	--
Wurtman, Richard (Phd neuroscience)	Milligan, McCall & Wurtman; Blusztajn & Wurtman; Pardridge & Oldendorf; Cohen & Wurtman; Ulus & Wurtman; Millington & Wurtman [recd 19 docts from counsel]	--	--	--