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Petition for Inclusion on the National List of Allowed Substances

Vantage™

OatVantage™ Oat Bran Concentrate

CBI Deleted Copy

600 Corporate Circle · Suite H · Golden, CO 80401 · 303-216-2489 · gtcnutrition.com

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October 10, 2007

Program Manager, USDA/AMS/TM/NOP
Room 4008-So., Ag Stop 0268
1400 Independence Ave., SW.
Washington, DC 20250
Phone: 202-720-3532
Fax: 202-205-7808

Dear Program Manager:

Please find enclosed duplicate copies of GTC Nutrition's petition to have OatVantage™, oat bran concentrate included on the National List of Allowed Substances in Organic Production. If you have any questions or need additional information please contact me directly.

Sincerely,

Luke R. Kazmierski
Quality Assurance and Regulatory Affairs Specialist
GTC Nutrition
Phone: 303-216-2489
E-mail: lkazmierski@gtcnutrition.com

1 Appendix 1
Petition Information

2 Appendix 2
Manufacturing Flow
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Item A:

Category: §205.606 Agricultural (nonorganic) nonsynthetic substances allowed in or on processed products labelled as "organic" or "made with organic (specified ingredients)."

Item B:

1. Common name of substance:
OatVantage™ (Oat Bran Concentrate), oat bran derived from oats, *Avena sativa*

2. Manufacturer's information:
GTC Nutrition
5840 Expressway
Missoula, MT 59808

3. Intended or current use:
Ingredient in food products

4. Handling activity:
OatVantage is normally added to other dry ingredients or liquids.

5. Source and manufacturing procedures:
The raw material is a naturally occurring oat bran derived from whole oats. The oat bran is milled to a concentrated form using a patented aqueous process. Please see attached flow chart (see Appendix 2).

6. Summary of previous regulatory reviews:
Oat bran has been approved by several regulatory bodies regarding health claims (see Appendix 4).

7. Information regarding regulatory registrations:
Oat bran is a well known food ingredient and Generally Recognized as Safe per 21 CFR 170.30(d) (see Appendix 5)

8. CAS number:
None

9. Chemical properties and mode of action

A) The substance, oat bran, is derived from whole oats and does not chemically react with other substances (see MSDS, Appendix 3).
B) There is no toxicity or environmental persistence as this is a naturally occurring oat bran source produced from whole oats.
C) This type of product has no significant effect on the human environment due to it being a naturally occurring oat bran source.
D) Effects on human health are attached (see Appendix 6). Generally the product is used for the improvement of human heart health.
E) Oat bran has no effect on soil organisms, crops or livestock.

10. Safety information:
MSDS attached (see Appendix 3)
GRAS Statement (see Appendix 5)

11. Research reviews provided:
The research reviews provided pertain to health benefits (see Appendix 6).

12. Petition justification statement:
The product falls under the category §205.606 Agricultural (nonorganic) nonsynthetic substances allowed in or on processed products labelled as "organic" or "made with organic (specified ingredients)." There are currently no organic equivalents of the product available. The product is not synthetic, it is a naturally occurring oat bran source produced from whole oats. Therefore OatVantage should be included on the National List, as it provides a valuable source of beta-glucan. OatVantage is easily incorporated into a wide range of foods, snacks, beverages and dietetic foods and leads to interesting documented health benefits at low inclusion levels.

13. Commercial confidential information statement:
The process flow chart for the manufacturing of OatVantage is considered confidential business information (CBI). This diagram is located in Appendix 2.

Category 1. Adverse impacts on humans or the environment? Substance: OatVantage

Question	Yes	No	N/A[1]	Documentation (TAP; petition; regulatory agency; other)
1. Are there adverse effects on environment from manufacture, use, or disposal? [§205.600 b.2]		√		**There is no toxicity or environmental persistence as this is a naturally occurring oat beta-glucan source produced from oat bran. Please see attached MSDS (See Appendix 3).**
2. Is there environmental contamination during manufacture, use, misuse, or disposal? [§6518 m.3]		√		**There is no toxicity or environmental persistence as this is a naturally occurring oat beta-glucan source produced from oat bran. Please see attached MSDS (See Appendix 3).**
3. Is the substance harmful to the environment? [§6517c(1)(A)(i);6517(c)(2)(A)i]		√		**There is no toxicity or environmental persistence as this is a naturally occurring oat beta-glucan source produced from oat bran. Please see attached MSDS (See Appendix 3).**
4. Does the substance contain List 1, 2, or 3 inerts? [§6517 c (1)(B)(ii); 205.601(m)2]		√		**There is no toxicity or environmental persistence as this is a naturally occurring oat beta-glucan source produced from oat bran. Please see attached MSDS (See Appendix 3).**
5. Is there potential for detrimental chemical interaction with other materials used? [§6518 m.1]		√		**This product is inert.**
6. Are there adverse biological and chemical interactions in agro-ecosystem? [§6518 m.5]		√		**This substance is intended as an ingredient in food products and exists in nature. The substance is GRAS (See Appendix 5). Please see attached MSDS (See Appendix 3).**
7. Are there detrimental physiological effects on soil organisms, crops, or livestock? [§6518 m.5]		√		**This substance is intended as an ingredient in food products and exists in nature. The substance is GRAS (See Appendix 5). Please see attached MSDS (See Appendix 3).**
8. Is there a toxic or other adverse action of the material or its breakdown products? [§6518 m.2]		√		**There is no toxicity or environmental persistence as this is a naturally occurring substance. Please see attached MSDS (See Appendix 3).**
9. Is there undesirable persistence or concentration of the material or breakdown products in environment?[§6518 m.2]		√		**There is no toxicity or environmental persistence as this is a naturally occurring substance. Please see attached MSDS (See Appendix 3).**
10. Is there any harmful effect on human health? [§6517 c (1)(A)(i) ; 6517 c(2)(A)i; §6518 m.4]		√		**There is no toxicity or environmental persistence as this is a naturally occurring substance. Please see attached MSDS (See Appendix 3).**
11. Is there an adverse effect on human health as defined by applicable Federal regulations? [205.600 b.3]		√		**This product is a naturally occurring source of oat beta-glucan which is GRAS (See Appendix 5).**
12. Is the substance GRAS when used according to FDA's good manufacturing practices? [§205.600 b.5]	√			**See GRAS statement (See Appendix 5).**
13. Does the substance contain residues of heavy metals or other contaminants in excess of FDA tolerances? [§205.600 b.5]		√		**This product is GRAS and does not exceed FDA tolerances (See Appendix 5).**

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

Category 2. Is the Substance Essential for Organic Production? Substance: OatVantage

Question	Yes	No	N/A[1]	Documentation (TAP; petition; regulatory agency; other)
1. Is the substance formulated or manufactured by a chemical process? [6502 (21)]		√		**This is a naturally occurring substance that is produced by milling oat bran. Please see attached flow diagram (See Appendix 2).**
2. Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral, sources? [6502 (21)]		√		**This is a naturally occurring substance that is produced by milling oat bran. Please see attached flow diagram (See Appendix 2).**
3. Is the substance created by naturally occurring biological processes? [6502 (21)]	√			**This is a naturally occurring substance that is produced by milling oat bran. Please see attached flow diagram (See Appendix 2).**
4. Is there a natural source of the substance? [§205.600 b.1]	√			**The substance exists in nature as oat bran found in oats.**
5. Is there an organic substitute? [§205.600 b.1]		√		**There are no known organic substitutes for oat bran.**
6. Is the substance essential for handling of organically produced agricultural products? [§205.600 b.6]	√			**The substance is essential for handling.**
7. Is there a wholly natural substitute product? [§6517 c (1)(A)(ii)]		√		**This is a naturally occurring oat bran product.**
8. Is the substance used in handling, not synthetic, but not organically produced? [§6517 c (1)(B)(iii)]	√			**This is a naturally occurring oat bran product that is used in handling, not synthetic and nonorganic.**
9. Is there any alternative substances? [§6518 m.6]		√		**The high concentration of oat beta-glucans cannot be found in any other products.**
10. Is there another practice that would make the substance unnecessary? [§6518 m.6]		√		**The high concentration of oat beta-glucans cannot be found in any other products.**

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

Category 3. Is the substance compatible with organic production practices? Substance: OatVantage

Question	Yes	No	N/A[1]	Documentation (TAP; petition; regulatory agency; other)
1. Is the substance compatible with organic handling? [§205.600 b.2]	√			**This substance is intended as an ingredient in food products. Studies have shown the numerous health benefits when consuming this product (See Appendix 6).**
2. Is the substance consistent with organic farming and handling? [§6517 c (1)(A)(iii); 6517 c (2)(A)(ii)]	√			**This substance is intended as an ingredient in food products. Studies have shown the numerous health benefits when consuming this product (See Appendix 6).**
3. Is the substance compatible with a system of sustainable agriculture? [§6518 m.7]	√			**This is a naturally occurring product.**
4. Is the nutritional quality of the food maintained with the substance? [§205.600 b.3]	√			**This substance improves the nutritional quality of foods in which it is added.**
5. Is the primary use as a preservative? [§205.600 b.4]		√		**The substance is intended as an ingredient in food with no preservative effect.**
6. Is the primary use to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk)? [205.600 b.4]		√		**This substance which is intended as an ingredient in food and is a natural source of oat beta-glucans.**
7. Is the substance used in production, and does it contain an active synthetic ingredient in the following categories: a. copper and sulfur compounds;			√	**This substance which is intended as an ingredient in food and is a natural source of oat beta-glucans.**
b. toxins derived from bacteria;			√	**N/A**
c. pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals?			√	**N/A**
d. livestock parasiticides and medicines?			√	**N/A**
e. production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleaners?			√	**N/A**

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

NOSB RECOMMENDED DECISION

Form NOPLIST2. Full Board Transmittal to NOP

For NOSB Meeting: _____ | Substance: _____

A. Evaluation Criteria (Documentation attached; committee recommendation attached)

		Criteria Satisfied?
1.	Impact on humans and environment	Yes ☐ No ☐ (see B below)
2.	Availability criteria	Yes ☐ No ☐ (see B below)
3.	Compatibility & consistency	Yes ☐ No ☐ (see B below)

B. Substance fails criteria?

Criteria category: _____

Comments:

C. Proposed Annotation: _____

_____

Basis for annotation:

To meet criteria above: ____ Criteria: _____

Other regulatory criteria: ____ Citation: _____

D. Final Board Action & Vote: Motion by: _____ Second: _____

Vote:

Yes: _____

No: _____

Abstain: _____

Agricultural		Nonagricultural		Crops	
Synthetic		Not synthetic		Livestock	
Allowed[1]		Prohibited[2]		Handling	
No restriction		Deferred4		Rejected[3]	

1—substance voted to be added as "allowed" on National List

Annotation: _____

_____

2—substance to be added to "prohibited" paragraph of National List

Describe why a prohibited substance: _____

_____

3—substance was rejected by vote for amending National List

Describe why material was rejected: _____

_____

4-substance was recommended to be deferred

Describe why deferred; if any follow-up is needed. If follow-up needed, who conducts follow-up. _____

_____

E. Approved by NOSB Chair to transmit to NOP:

_____ _____

Dave Carter, NOSB Chair Date

F. NOP Action: Include in FR to amend National List: ☐

Return to NOSB ☐ Reason: _____

_____ _____

Richard H. Mathews, Program Manager Date

NOSB COMMITTEE RECOMMENDATION

Form NOPLIST1. Committee Transmittal to NOSB

For NOSB Meeting: _____ Substance: _____

Committee: Crops ☐ Livestock ☐ Handling ☐

A. Evaluation Criteria (Documentation attached; committee recommendation attached)

	Criteria Satisfied?
4. Impact on humans and environment	Yes ☐ No ☐ (see B below)
5. Availability criteria	Yes ☐ No ☐ (see B below)
6. Compatibility & consistency	Yes ☐ No ☐ (see B below)

B. Substance fails criteria?

Criteria category: _____

Comments:

C. Proposed Annotation: _____

Basis for annotation:

To meet criteria above: ____ Criteria: _____

Other regulatory criteria: ____ Citation: _____

D. Recommended Committee Action & Vote: Motion by: _____

Seconded: _____

Vote:

Yes: _____

No: _____

Abstain: _____

Agricultural		Nonagricultural		Crops	
Synthetic		Not synthetic		Livestock	
Allowed[1]		Prohibited[2]		Handling	
No restriction		Deferred4		Rejected[3]	

1—substance voted to be added as "allowed" on National List

Annotation: _____

2—substance to be added to "prohibited" paragraph of National List

Describe why a prohibited substance: _____

3—substance was rejected by vote for amending National List

Describe why material was rejected: _____

4-substance was recommended to be deferred

Describe why deferred; if follow-up is needed. If follow-up needed, who will follow up _____

E. Approved by Committee Chair to transmit to NOSB:

_____ _____

Committee Chair Date

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OatVantage™ Manufacturing Process Flow – CBI Deleted

CBI Deleted

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Material Safety Data Sheet

Version: 2/14/2007

1 - IDENTIFICATION OF PRODUCT AND COMPANY

Name of Product:	***OATVANTAGE™ OAT BRAN CONCENTRATE***
Supplier:	GTC Oats
Address:	5840 Expressway Missoula, MT 59808 USA
Phone:	406-541-6382
Fax:	406-541-6383

2 - COMPOSITION / INFORMATION ON COMPONENTS

Preparation:	Derived from natural sources (oats) by a specialized process
Substance:	Beta-glucan, protein, starch, fiber, and residual lipids
Hazardous ingredients:	None
Preservatives:	The material contains no added antioxidants or antimicrobial preservatives

3 - IDENTIFICATION OF HAZARDS

Main hazards:	Material is a powder, consisting predominantly of organic particles with a median diameter of approximately 150 microns. Consequently, exposure to spark or flame in an atmosphere laden with the dust could result in an explosion.

4 - EMERGENCY AND FIRST AID PROCEDURE

Inhalation:	Remove from exposure and supply fresh air. If breathing has stopped, administer artificial respiration and oxygen if available. Contact a physician as necessary.
Eye Contact:	Flush immediately with clean water for at least 15 minutes. Contact a physician as necessary
Oral:	None, this product is intended for human consumption. Any food product may cause choking.
Skin:	Wash with soap and water.

5 - SPECIAL FIRE FIGHTING PROCEDURES

Extinguishing Media:	Carbon Dioxide, Dry Chemical, or Foam
Special Fire Fighting Procedures:	None
Unusual fire and Explosion Hazards:	Risk of dust explosion if mixture of dust and air are ignited in a confined space

6 - STEPS TO BE TAKEN IN CASE OF SPILL

Eliminate all ignition sources. Wear proper safety equipment including eye, respiratory and skin protection. Contain spill and recover free product. Collect and package for proper disposal according to local regulations. Report spills to appropriate authorities if required.

7 - HANDLING AND STORAGE

Handling:	Keep containers tightly closed and upright when not in use.
Storage:	Store in a cool, dry, area away from any heat sources.

8 - SPECIAL PROTECTION INFORMATION

Eye Protection:	Use splash goggles or face shield when eye contact might occur.
Respiratory Protection:	None generally required. If desired, use NIOSH approved respirator.
Ventilation:	Local exhaust meeting ACGIH criteria as needed.
Work/Hygienic Practices:	Avoid inhalation and contact with eyes. Good personal hygiene practices should be used.

9 - PHYSICAL / CHEMICAL PROPERTIES

Boiling Point:	Not Applicable (Solid material)
Melting Point:	None, material does not melt
Bulk Density:	>0.65 grams per milliliter
Solubility in Water:	Mostly soluble
Appearance/Odor:	Beige powder, characteristic oat odor
Vapor Pressure:	Not Applicable
Vapor Density:	Not Applicable
Percent Volatile (@70° F):	ca. 0%
Evaporation Rate:	Not Applicable

10 - STABILITY AND REACTIVITY

This product presents no significant reactivity hazard. It is stable and will not react violently with water. Hazardous polymerization will not occur. Avoid contact or contamination with strong acids, alkalis, or oxidizing agents. Carbon monoxide and unidentified organic compounds may be formed during combustion.

11 - TOXICOLOGICAL DATA

No acute or chronic toxic effects expected when used according to directions. May be irritating, to eyes, throat, and lungs.

12 - ECOLOGICAL DATA

This material is derived from natural sources and is not chemically altered. NTP, IARC, or OSHA lists none of the components as carcinogens or potential carcinogens.

This material is completely biodegradable.

13 - WASTE DISPOSAL METHODS

Destruction/Elimination:	Place material into sealed containers and dispose of in accordance with current applicable laws and regulations.
Soiled packaging:	As above (caution: there may be local regulation to be observed)

14 - TRANSPORT INFORMATION

Not classified as a hazardous material.

15 - OTHER INFORMATION ON REGULATION

Labelling:	No specialized labelling requirements apply, not regulated by EEC regulation.

16 - FURTHER INFORMATION

None

"This sheet is a complement to technical directions for use documents but it does not replace them. Information mentioned on this sheet is based on our present knowledge on the product concerned, at the date mentioned. It is given in good faith. Moreover, the attention of the user is drawn on the possible hazards linked to the use of the product for other uses than the ones it is intended for".

"This sheet does not exempt the user from knowing and applying all the regulations relevant to his activity. The user will be sole responsible for respecting the precautions linked to the use of the product".

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OatVantage™ Regulatory Claims Approvals

1997 – U.S. FDA Heart Health Claim (21 CFR 101.81)

2001 – Sweden – Swedish Nutrition Foundation

2002 - Sweden – Swedish Nutrition Foundation

2004 – United Kingdom – Joint Health Claims Initiative

2005 – Netherlands – Voedingscentrum

2006 – Switzerland – Federal Office of Public Health

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April 17, 2007

Re: GRAS (Generally Recognized as Safe) Status of OatVantage™

Dear Valued Customer,

Oat bran is Generally Recognized as Safe (GRAS) under 21 CFR 170.30(d). In addition, an independent panel of recognized experts, qualified by their scientific training and relevant national and international expertise in evaluating the safety of food ingredients, evaluated OatVantage scientific literature, manufacturing procedures, product specifications, proposed uses, exposure and safety information and determined it is GRAS when produced and used in accordance with current Good Manufacturing Practices (cGMP).

Sincerely,

Luke R. Kazmierski
Quality Assurance and Regulatory Affairs Specialist

600 Corporate Circle ● Suite H ● Golden, CO 80401 ● 800-522-4682 ● www.gtcnutrition.com
A business unit of Corn Products International, Inc.

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Oat Fiber

Production, Composition, Physicochemical Properties, Physiological Effects, Safety, and Food Applications

Yrjö Mälkki
Cereti Ltd., Espoo, Finland

I. INTRODUCTION

By tradition, oats have been used as human food since ancient times and have been a staple food in many countries. It has been regarded as a healthy food without a clear knowledge of its specific health-related effects. However, today we know that its effects on satiety and retarded absorption of nutrients and as a deterrent of various disorders of the gastrointestinal tract account for this reputation. These beneficial effects are a result of oats soluble fiber content. Today oats are one of the richest and most economical sources of soluble dietary fiber; they also contain insoluble fiber.

The present interest in soluble oat fiber originated from animal and human studies of de Groot et al. in 1963 (1), which showed a hypocholesterolemic effect of relatively massive amounts of rolled oats. This launched an extensive series of both animal and clinical studies, the majority of which confirmed this effect. However, not until 1988 was public attention drawn to the possibilities of exploiting this effect therapeutically. An econometric study (2) based on the available clinical studies indicated potentially drastic cost savings using oat bran–based treatments as compared to chemotherapy.

The use of oats as food in the United States increased during 1985–1990 2.5-fold (3). This so-called oat boom was suddenly interrupted as a result of a well-publicized but less well-planned and performed study (4), which did not find a hypocholesterolemic effect of oat fiber. Although serious drawbacks of this study were soon indicated in the scientific journals by several authors, the demand for oat bran decreased somewhat but remained elevated level during the 1990s (5) and is again increasing since the allowance of health claims in the marketing.

In other industrialized countries the interest in the effects of oat soluble fiber has followed the same trend, but changes in the demand have been more modest. In addition to oats' hypocholesterolemic effect, focus on other physiological effects, in particular on hypoglycemic effect, started gradually to grow.

In addition to oat bran fiber, products made from oat hulls are also on the market. Their fiber is nearly entirely insoluble. They are used in the food industry mainly as a water-binding and structure-giving ingredient and have less and different physiological effects than oat bran fiber.

II. PRODUCTION AND CONSUMPTION OF OATS

The principal oat species cultivated and marketed today are *Avena sativa* (white oats) and *Avena byzantina* (red oats). The principal oat-producing areas in 1997, in order of magnitude of production, were Russia, the European Union, Canada, the United States, central Europe, and Australia. The principal oat-exporting countries are Canada, Sweden, Finland, and Australia. Of the total amount produced, 23% is used globally for food. The per capita consumption (kg/year) is highest in Russia (12.0), Canada (8.5), Australia (8.1), the Scandinavian countries (4–6), and the United States (5.2) (5). Dietary fiber obtained from these amounts is 0.6–1.7 g/day, but since individual consumption of oats varies greatly, regular users of oat products can obtain a substantial part of their total and soluble dietary fiber intake from oats.

III. AMOUNT AND LOCATION OF FIBER IN THE OAT KERNEL

Of the total weight of oat kernels of common cultivar varieties, 20–35% consists of hulls, which in an unprocessed state contain approximately 85% insoluble dietary fiber. Exceptions are naked cultivar varieties, where the hull content is less than 5%. Hulls can be further processed to bleached oat hull fiber, which has a dietary fiber content of more than 90%, all of it being insoluble.

In the remaining edible part, the groat, the total content of dietary fiber is usually 6–9%, about half of which is insoluble fiber, located mainly in the tissues outside the aleurone layer (Fig. 1). The principal component of the soluble fiber is a linear polysaccharide (1 → 3),(1 → 4)-β-D-glucan, usually called β-glucan. It is located in endosperm cell walls, which are thickest adjacent to the aleurone layer, in the subaleurone layer. However, the size of endosperm cells, the thickness of the cell walls throughout the groat, and thus the distribution of β-glucan vary widely among the different cultivar varieties (6).

The total β-glucan content of oat groats is influenced by both genetic and environmental factors, the genetic influence being the greatest (6–10). Reported contents vary from 1.8 to 8.5%, but the varieties having the highest β-glucan content are not commonly cultivated, and in the oat trade the content of β-glucan usually varies from 3.5 to 5.5%. Cultivar varieties that develop large kernels usually also have a high β-glucan content, and there is a negative correlation between the protein and β-glucan contents (9,11).

The effects of environmental conditions are less clear, and some effects observed are valid only for some of the varieties commonly cultivated. This might at least in part be due to the fact, that an effect on the β-glucan level can be indirect and affected by several simultaneously contributing factors. All the published cultivation studies have been made under field conditions, and thus have been subject to the natural variation of weather and soil conditions.

The effect of growing location—often a combined effect of climatic conditions and soil type—is evident. Studies from Germany (12) and Australia (13) show that on average the growing location can cause a difference of 0.3–0.7% units in the β-glucan content. In both German (12) and Finnish studies (14) the influence of the harvest year conditions outweighed the influence of location.

A highly significant correlation ($p < 0.001$) between the mean temperature of growing time and the content of β-glucan has been reported (14). There is a negative correlation between the content of β-glucan and the growing time, as measured from time of sprouting to ripeness (7). The effects of rainfall are complicated. A negative correlation often reported (14) could be caused by the fact that under dry growing conditions the ripening of the kernel starts prematurely

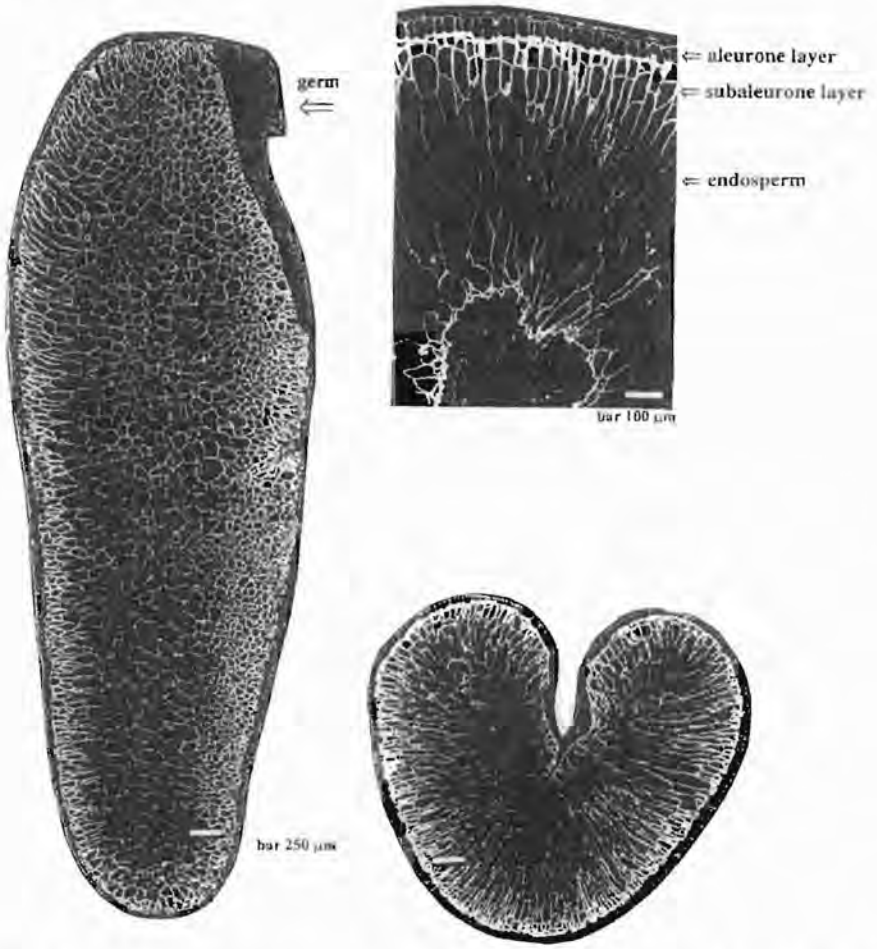

Fig. 1 Structure of oat groat. β-Glucan is located in the white cell walls of the inner endosperm and subaleurone layer. (Micrographs courtesy of Dr. K. Autio, VTT Biotechnology, Espoo, Finland.)

and leads to a small kernel size in which the relative amount of fiber-rich outer layers is higher.

Relatively high values of β-glucan are obtained on soils with low but not excessively low pH value (14). A high phosphorus content limits the β-glucan content (14), possibly by favoring an increase in phytic acid, which has a negative correlation with β-glucan content (15).

IV. PROCESSING

A. Hulling

After pretreatments for cleaning and grading, the first stage of the conventional oat milling process is hulling, where the outer layers of the kernel are removed by impact and aspiration treatments (16,17). Hulls as such do not contain soluble fiber, but any hulling loss exceeding the share of hulls also means losses of soluble fiber into the hull fraction.

B. Heat Treatments

Heat treatments serve several purposes. Dry heat treatments are used for creating a roasted flavor and/or, when performed before hulling, for enhancing the release of hulls. Hydrothermal treatments serve to inactivate enzymes, especially lipase and lipoxygenase, which can cause rancidity and a bitter taste, and β-glucanase and to improve the solubility of β-glucan.

A conventional hydrothermal treatment involves steaming and dry heating at 95–105°C for 0.5–2 hours. The process parameters are chosen based on the known time-temperature dependence of enzyme inactivation (16,18). The process is usually controlled by determining residual tyrosinase activity as an indicator for inactivation of lipase and lipoxygenase. A more effective stabilization and simultaneously hydratation of β-glucan is achieved by mild heat treatments under pressure. For controlling inactivation of β-glucanases, the most relevant method in regard to preserving the physiological activity is to test the absence of a viscosity-reducing effect in suspensions of hydrated β-glucan–containing material.

C. Oatmeal and Rolled Oats

Traditional oat flakes are prepared from hulled and heat-treated groats by rolling between cast-iron rolls that have equal speeds. This is typically performed immediately following steaming, which serves both to enzyme inactivation and for plasticising the groats. More rapidly cooking flakes and instant oat flakes are prepared by steel-cutting the groats in three to five pieces before rolling, by decreasing the flake thickness, and by more intensive steaming.

Traditional whole oat flour is prepared from oat groats by milling. When further treated by removing bran fractions by sieving, the resulting flour is called refined oat flour. For details of the preparation see Ref. 17.

D. Oat Bran

In contrast to many other cereal materials, oat bran does not consist of a sharply limited distinct part of the oat groat. In conventional milling operations, the subaleurone layer, which consists of thick-walled cells (see Fig. 1), follows the coarse outer layers of the groat and is thus included in the bran.

In the United States, the following definition for oat bran is valid (19): "Oat bran is produced by grinding clean oat groats or rolled oats and separating the resulting oat flour by suitable means into fractions, such that the oat bran fraction is not more than 50 percent of the original starting material and provides at least 5.5 percent (dwb) β-glucan soluble fiber and a total dietary fiber content of 16 percent (dwb), and such that at least one-third of the total dietary fiber is soluble fiber."

In conventional oat milling processes, hulled and heat-treated oat groats are subjected to grinding and sieving operations in one or several stages to separate the major part of starchy endosperm from the outer layers of the groat. Bran is separated as the coarse fraction. A practical upper limit for β-glucan in the traditional milling process is 10%; in commercial oat brans the content varies from 5.5 to 9%. The present industrial practice has been reviewed in Refs. 17 and 20.

E. Dry Enrichment of Oat Fiber

To enable physiologically effective amounts of oat soluble fiber to be ingested without simultaneously ingesting excessive amounts of other oat constituents, efforts to concentrate oat fiber

further from oat bran or oat flour have been made since that late 1980s. Preparations from an unexplained "nonsolvent fractionation" process containing 10.9–12.3% β-glucan (21,22) have been supplied to animal studies. In published laboratory and pilot-scale dry fractionations (23), brans containing up to 12.8% β-glucan have been obtained. In recent studies (Y. Mälkki and O. Myllymäki, unpublished), the highest contents of β-glucan in enriched full-fat bran in laboratory and pilot-scale experiments were 17.5 and 16.1% of dry weight, respectively.

F. Concentrations After Defatting or in Organic Solvent

To avoid difficulties in clogging and material flow caused by fat content, several groups have used defatting of oat groats or flakes and subsequently performed grinding and sieving or air classification operations in a dry state. After defatting with hexane, pin milling or abrasive milling and air classifications, concentrated brans containing 11.2–30% β-glucan have been achieved (23–25). A disadvantage in the dry sieving operations is the transfer of β-glucan into the fine fraction, which reduces the yields of concentrates obtainable. By sieving in aqueous or organic solvent, sieves with smaller openings can be used and thus losses of β-glucan into the fine fraction reduced. In earlier studies (for review, see Ref. 20) the point was mainly to separate protein, and the most common solvent was hexane. Contents of β-glucan were not analyzed, but as now estimated from the yield of the bran fraction, concentrations of β-glucan have probably been between 8 and 12%. In later studies using ethanol or 2-propanol as a solvent (23,26), β-glucan concentrations in the coarse fraction could be elevated up to 15–18% and even up to 27%. (Y. Mälkki and O. Myllymäki, unpublished).

A concentration of oat fiber based on soaking groats in 50°C water and a subsequent wet milling in ethanol has been presented (27). According to the patent specification, the content of β-glucan in the final bran fraction is 19.4%; in the commercial product it is declared to be more than 16% (28). At the time of the manuscript of this paper, the product is marketed mainly to the cosmetic industries.

A method for concentration of β-glucan to 30% or even 40% level has been developed (29). It is based on a hydrothermal treatment with or without a combination with enzymatic degradation of protein and removal of starch by further sieving. Simultaneously, the solublity of β-glucan is improved.

G. Aqueous Processes

In an aqueous wet milling process (30), use is made of the low and slow solubility of β-glucan in cold water, and starch is removed by a rapid screening of oat flour in cold water. In the patent description the content of β-glucan was said to be 31%; in the commercial product it was 15%. Marketing of this concentrated bran was discontinued in 1996.

Concentration of soluble fiber by removal of insoluble fiber is used in an enzymatic process (31). Oat flour or oat bran is hydrolyzed by thermostable α-amylases to convert the starch into maltodextrins, and β-glucan is dissolved. Insoluble components are separated by centrifugation. Commercial preparations have found a market mainly based on the properties of maltodextrin; the β-glucan content in the different preparations varies from 1 to 20%.

H. Isolation of β-Glucan

Methods presented are based on the well-known solubility of β-glucan in hot water and in alkaline solutions, separation of the dissolved proteins by isoelectric precipitation, and precipitating the β-glucan by ammonium sulfate, 2-propanol, or ethanol (32,33). Preparations usually

contain 60–80% β-glucan, the remaining part being mainly protein (7–22%), mineral substances (3%), pentosans, starch, and lipid (0.1–1.0%) (34,35). Since 1996 isolated β-glucan has been produced on a small scale for cosmetic, skin care, and immunological applications. In further purification for research purposes, repeated precipitations and enzymatic hydrolysis of residual starch are used, and a purity of 99% has been reached (35).

I. Oat Hull Fiber

A minimal process is to grind and sieve the material to obtain a particle size of 0.2–0.4 mm. Another type of preparation involves bleaching with alkaline hydrogen peroxide to dissolve partially the lignin (36). The process reduces the original tan color, improves the speed of hydratation and water-holding capacity, and reduces the gritty mouthfeel of the untreated material.

V. CHEMICAL STRUCTURE

A. β-Glucan

The main component of oat soluble fiber, β-glucan, is a linear polysaccharide composed of (1 → 3) and (1 → 4)-β-linked glucosidyl subunits (Fig. 2). (1 → 3) linkages occur singly, linking together (1 → 4)-β-linked oligosaccharidyl subunits. Structurally related mixed-linkage β-D-glucans differ in the ratio of tri-and tetrasaccharidyl residues, which for β-glucan of oats is 2.1–2.4, for barley 2.8–3.3 (37), and for wheat 3.0–3.8 (35). Other frequently occurring sequences have a degree of polymerization (DP) of 5 or 9, but sequences with a DP up to 15 have been found (37).

Isolated and purified β-glucan frequently contains 0.5–1% or even more nitrogen, which usually is interpreted to derive from proteins, peptides, or amino acids. It is still uncertain whether protein or peptide is covalently bound to the β-glucans (38). It may bind β-glucan to the cell wall structure, as has been suggested for barley (39), or it may bind macromolecule chains to each other. An indication for binding is the reduction of viscosity by trypsin (40), which is dissimilar in different cultivar varieties (41).

The highest peak molecular weights, $2.9–3.1 \times 10^6$ daltons, have been reported for β-glucan extracted in sodium carbonate solutions from ground oat groats or oat bran (42). These values are higher than those found for β-glucan from barley ($1.3–2.7 \times 10^6$), waxy barley ($1.3–1.5 \times 10^6$) or rye (1.1×10^6) (42). In commercial oat products, the peak molecular weights have varied from 0.6 to 3.0×10^6 daltons. In commercial oat brans the peak molecular weight in hot water extracts varied from 1.4 to 1.8×10^6 daltons, and in an extract made by simulating physiological conditions from 1.1 to 1.9×10^6 daltons (43).

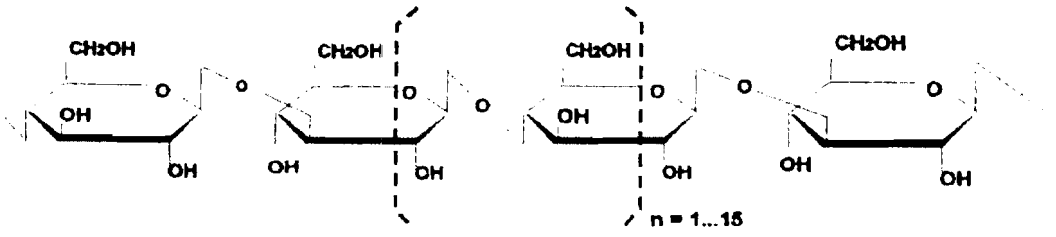

Fig. 2 Structure of oat β-glucan, (1 → 3),(1 → 4)-β-D-glucan.

A drastic decrease in molecular weight can occur in isolation procedures, on both a laboratory and technical scale, and in technical processing (23). Factors affecting a reduction are temperature, alkalinity, acidity, shear forces, and enzymatic breakdown. In isolated β-glucan weight average molecular weights have varied from 0.7 to 1.63 × 10^6 daltons (42), and in physiological extracts of oat bran muffins peak molecular weights vary from 0.6 to 1.2 × 10^6 daltons (43). In breads weight average molecular weights from 0.5 to 2.0 × 10^6 daltons have been found (44; T. Suortti, personal communication). Incubation of unheated oat bran for 0.5 hour at pH 5 and room temperature is sufficient to reduce the molecular weight from 1.5 × 10^6 to 3.7 × 10^5 daltons (40) The molecular weight has also been found to decrease during storage of ground oat material in a dry state, even in frozen storage (45).

B. Oat Hull Fiber

Unprocessed oat hull fiber typically contains 70–75% carbohydrates, the remaining part being protein, lignin, and ash. The content of cellulose is reported to be 30.9%, that of other hexosans 2.6% and of pentosans 33.2% (46). In bleached hull fiber, the carbohydrate content is usually above 90%.

VI. PHYSICAL PROPERTIES

A. Water Solubility and Extractability of β-Glucan

The "final rule" for food labeling health claims (19,47) refers to "β-glucan soluble fiber" and to an enzymatic method for the determination of β-glucan (48), which does not differentiate between soluble and insoluble β-glucan. For declaration purposes, valid standard methods for soluble dietary fiber must be applied, although all of these (49) involve an initial heating step and thus do not as such simulate physiological conditions.

Solubility of β-glucan is dependent, on the one hand, on the pretreatment of the preparation and, on the other hand, on the extracting conditions. Dissolving of β-glucan occurs gradually, the principal factors being temperature, moisture content, possible barriers for water penetration and for diffusion of the dissolved material, and the possible presence of endogenous or microbial enzymes degrading the macromolecules.

In studies in which unheated oat grain samples or commercially heated oat bran have been extracted at 38 or 40°C (40,50,51), 79.5–90% of β-glucan has been extractable. Under the same conditions, only 40.4–44.0% of β-glucan was extracted from hot-ethanol wet milled oat bran concentrates (40). The difference is probably due to the solubilization of β-glucan by the endogenous enzymes. At 80°C, the extractability of β-glucan from an ethanol enzyme-inactivated material was 46% (42) and at 90°C in water containing thermostable α-amylase 72–79% (52). As expected, milling treatments and particle size have a great influence on the extractability, not only by increasing the contact surface of the solid particle and water, but also by opening the physical barriers of the plant tissue structure for water penetration.

Extractability of β-glucan under simulated physiological conditions has been found to be from oat brans 12.9–28.7%, from rolled oats 33.2%, and from oat bran muffins 30.3–85.3%, the latter depending on the formulation and starting material (43). The solubility of β-glucan in muffins decreased in frozen storage (−20°C) during 8 weeks to about a half of the starting value: "the decline in solubility . . . possibly reflects changes in molecular organization and crystallinity" (43). These changes might be similar to those leading to the decreased solubility of ethanol enzyme inactivated samples. No studies exist on the reversibility of these changes.

B. Rheological Properties

At low shear rates (<10/s) or frequencies, the apparent viscosity of aqueous solutions of unhydrolyzed oat gum is independent of shear rate, which indicates no macromolecular interactions (53). At higher shear rates and above a concentration of 0.2% the solutions are shear-thinning but do not exhibit a time-dependent behavior. Starting from concentrations of 0.3–0.4%, the viscosity increases very steeply, and the concentration dependency is similar to that of guar gum (53). The viscosity level is sensitive to changes in molecular weight. Thus, e.g., β-glucan concentrations needed to give an apparent viscosity of 200 mPa·s at a shear rate of 30/s were 0.58, 1.39, and 5.5%, when the weight average molecular weights were 1.2, 0.36, or 0.1×10^6 daltons, respectively (53). The viscosity is not affected by sodium chloride but is increased by 25 and 50% sucrose concentrations (54).

Micelle-like aggregations have been observed with low molecular weight oat gum preparations (53,55), and these can lead either to a suspension or to a weak network (53). Aggregations are not found with unhydrolyzed preparations (53). Oat maltodextrin containing 10% of β-glucan exhibited in a 5% suspension a shear thickening behavior at shear rates from 20 to 80/s, returning to the shear thinning behavior again at higher shear rates, whereas cooked oat bran showed constantly a shear thinning behavior (56).

In suspensions of β-glucan–containing oat products, the viscosity is for the main part determined on the amount of β-glucan dissolved from the material and its molecular weight. Less refined and not intensively heat-treated oat products give lower viscosities, which also develop slowly, but the viscosity can be drastically increased by hydrothermal treatments. Losses of viscosity during isolation procedures are most probably mainly due to shear forces involved. Losses in bread baking are mainly due to hydrolysis by β-glucanase enzymes deriving from yeast, contaminating microorganisms, or other cereal ingredients (57) but can also be in part due to thermal degradation (44). Contaminating microorganisms are an important source of endogenous β-glucanases (58).

Diminution of particle size improves water penetration, as stated above, but the rapid water absorption can lead to caking and clogging effects and to the so-called fish-eye formation, in which the outer layers of an agglomerate absorb water, forming a heavily viscous layer that delays diffusion of additional water for hydrating the inner parts of the agglomerate. This effect can be prevented by, for example, mixing the β-glucan–containing preparation with inert materials such as maltodextrin (59) or by precipitating the β-glucan during the preparation on an inert material (29).

Enzymatic degradations of several components of the material often initially elevate the extractability of β-glucan, but they usually lead to reduced viscosities due to the breakdown of β-glucan macromolecules.

Table 1 Water Hydration Capacity of Some Natural and Processed Fibers

Fiber source	Water hydration capacity (g/g dry substance)	Ref.
Cellulose	4.7	Opta Food Ingredients, Bedford, MA
Wheat bran	1.67	20
Oat hull fiber	1.76	20
Oat hull fiber HDF-90	6.0–7.0	National Oats, Cedar Rapids, IA
Oat bran, commercial	4.12	20
Oat bran, experimental	7.76	20, 23
Oat bran, experimental	12.74	20, 27

C. Water Binding

Both soluble and insoluble fiber affect the water-binding capacity of oat fractions. This alters the behavior in the processing as well as properties of the products. Representative data are presented in Table 1. As expected, the hydration capacity increases with increasing content of β-glucan, but it is also greatly improved by hydrothermal treatments (not shown). In preparations with the highest hydration capacities there is a gradual transition to viscous suspensions.

VII. PHYSIOLOGICAL EFFECTS

A. Cholesterol and Lipid Metabolism

1. Occurrence and Magnitude of the Effect

Reduction of blood total and low-density lipoprotein (LDL) cholesterol are the most well-known physiological effects of oat soluble fiber. It is unanimous that the principal causative component is oat β-glucan, although effects of other components are not excluded.

Three recent reviews of the clinical studies on this effect are available. A meta-analysis (60) covering 20 original studies, all of which were randomized and controlled, resulted in the following conclusions:

Initial cholesterol level	Change, β-glucan < 3 g/day	Change, β-glucan ≥ 3 g/day
<5.9 mmol/L	0.09 ± 0.10 mmol/L	0.13 ± 0.12 mmol/L
≥5.9 mmol/L	−0.27 ± 0.04 mmol/L	0.41 ± 0.21 mmol/L

Earlier metabolic studies as well as recent human and animal studies and the mechanism of action are reviewed in Ref. 61. The U.S. Food and Drug Administration (FDA) (62) reviewed 37 clinical studies in view of the significance and dose-response of the effect. On this basis, FDA later (19,47) authorized the use of health claims addressing the association between soluble fiber from whole oats and a reduced risk of coronary heart disease. Preconditions for the claim are that the product should contain at least 0.75 g of β-glucan soluble fiber per serving and that the β-glucan soluble fiber is derived from whole oats.

To determine the dose response based on the total existing experimental material, a literature survey was made without prescreening the studies. Fifty-three original clinical studies were identified, 37 of which reported a significant reduction of cholesterol, 10 others a nonsignificant reduction. The reason for nonsignificance was often the small number of subjects who participated in the study; several of these studies showed a mean reduction of more than 8%. However, the dose response was very scattered (Fig. 3). Below an evident threshold of 3 g β-glucan a day, the reduction of cholesterol was minimal, after which a trend for dose response is evident. As a rule, the reason for a weak response or for no effect has been one or several of the following:

A too low β-glucan content in the experimental diets
A low solubility of β-glucan, e.g., use of unheated oat bran
A weak compliance to the prescribed intake of soluble fiber
Participation of subjects with initially low blood cholesterol
Participation of subjects nonresponding for genetic reasons
Faults in the experimental design

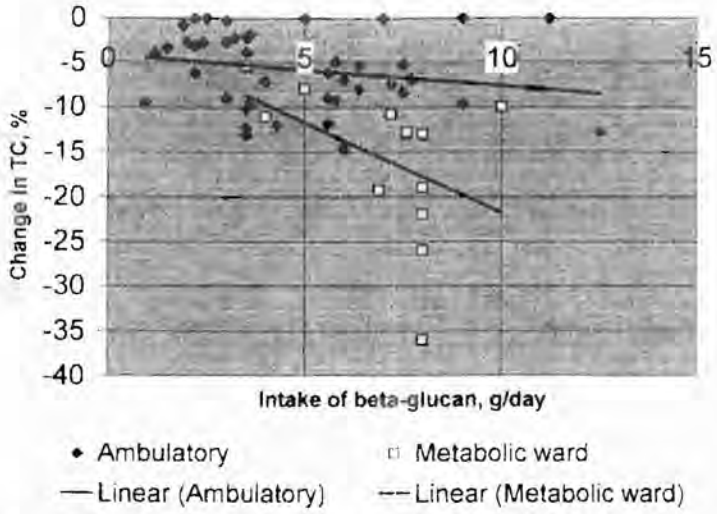

Fig. 3 Dose response of the cholesterol-lowering effect of β-glucan in 53 clinical studies published between 1963 and 1998. In cases where the amount of β-glucan has not been given in the original paper, it has been estimated on the basis of the average content of β-glucan in the components of the experimental diet.

The great difference in the dose response between the ambulatory and metabolic ward studies shown in Fig. 3 is evidently caused partly by the better control of compliance and partly by the route of administration. In most of the metabolic ward studies, oat soluble fiber has been given as porridge or as oat muffins, thus in both cases in a prehydrated state, which has enabled a rapid development of viscosity in the stomach and in the upper small intestine. In many of the ambulatory studies the oat preparation has been given to the subjects in a dry state; its further preparation or intake in a dry state has varied among the test subjects, and control of leftovers has in most cases been lacking or insufficient. The trend of ambulatory studies thus does not give a true picture of the dose response.

Due to the commercial unavailability of preparations, only a few studies have been made using isolated β-glucan. In one of them (63) a dose of 2.9 g of β-glucan twice daily for 4 weeks was used. The test subjects had an average baseline blood total cholesterol of 6.77 mmol/L. A reduction of 9.2% in total cholesterol and 10.0% of LDL cholesterol was observed. Five of the 19 subjects proved to be nonresponders. In another study (64), no reduction of cholesterol was observed despite a daily dose of 9 g of β-glucan. Possible reasons for the lack of effect on total cholesterol are a verified reduction of molecular weight of β-glucan in the isolation (65) and the low initial serum cholesterol content (4.23 mmol/L) of the subjects.

Data on the effect of oat β-glucan obtained from other concentrated sources show varying responses. A ready to eat (RTE) cereal made from a concentrated oat bran prepared by an undisclosed "nonsolvent process" gave with a similar dose of β-glucan a reduction of total cholesterol similar to that of oat bran (66), but was in rat studies more effective than oat bran (21,22,67). Oat bran concentrates made by ethanol wet milling, used at a level of 9 g β-glucan a day, gave a reduction of total cholesterol of 13.6% and of LDL cholesterol 23% (68). The same preparation showed in two rat studies (40,69) higher responses than oat bran with a similar dose of β-glucan. Oat fiber extracts prepared by the enzymatic method (31) given at levels corresponding to 0.95 or 6.0 g β-glucan a day caused reductions in total cholesterol of 9.5 or

14.6%, respectively (70). Oat bran concentrates prepared by an aqueous wet milling process were less effective than oat bran. In two clinical studies with daily doses of β-glucan of 10.3 or 11.2 g, a reduction of cholesterol was observed after 4 weeks, but after 8 weeks the cholesterol levels returned to near the initial level (71,72). The weak response has most probably been due to a weak solubility of β-glucan and to the weak viscosity properties of the water-soluble fraction of β-glucan (40).

Individual responses have in at least 12 clinical studies been reported to show nonresponding subjects, reports of the share of such persons varying from 20 to >50%. Different responses have been in a few studies related to apolipoprotein E polymorphism, but the results are controversial (71,73,74; Å. Lia et al., unpublished). The subject has been reviewed briefly (75).

2. Mechanism of Action

The reduction of cholesterol is evidently a sum of several effects. However, it is a commonly accepted concept the main part of the effect is due to the decreased absorption of bile acids, which causes a removal of steroids from the body by fecal excretion. The probable main consequence is an increased catabolism of cholesterol, an increase in the secretion of bile acids (76), a decrease in lipoprotein cholesterol secretion, and a reduction in the total body pool of cholesterol.

Direct indications of this mechanism are an increase in excretion of bile acids via feces: reported increases of bile acid excretion vary from 35 to 65% (77–80). There is no direct proof for a mechanism of the reduced absorption, but it is probably for the main part caused by the increased viscosity in the small intestine. This explanation is supported merely by the physical effect of the viscosity on the diffusion rates and the thickness of the unstirred layer on the site of absorption, but also by a study on cholesterol and galactose absorption in rat small intestine in vitro (81). This is related to the effects of β-glucan and its viscosity on the absorption of glucose (59).

Due to a decrease in bile acid content in the small intestine, emulsification of fats is decreased, which in addition to the viscosity effects mentioned reduces fat absorption. As a result, excretion of fat is increased. In a study with ileostomies (80) this excretion was 5.5 g/day, which does not significantly alter the amount of fat available daily but might have a positive long-term effect. Reduction and retardation of absorption of nutrients can also have effects via hormonal pathways.

Less attention has been paid to a possible role of apolipoprotein B_{100}. This is the major structure protein of LDL cholesterol and the binding site for the LDL receptor. In one study (82) oat bran reduced its content by 25%, while LDL cholesterol was simultaneously reduced by 10.5%. Elevated levels of $apoB_{100}$ are known to be a risk factor for coronary heart disease. Additional experimental data are needed to confirm this effect and to evaluate its relative importance for reducing the risk of coronary heart disease.

A suggested mechanism for cholesterol reduction is the action of short-chain fatty acids. Soluble fiber entering the colon is fermented nearly completely, the main end products being acetic, propionic, and butyric acids. Since propionic acid inhibits cholesterol synthesis in isolated rat hepatocytes at concentrations of 1.0–2.5 mM (83), it has been suggested that it would have an inhibiting effect on liver cholesterol synthesis. However, in rats fed oat bran the concentration of propionate in the hepatic portal vein has been shown to be maximally 0.35 mmol/L (76), and this mechanism seems thus to be unlikely or have a minor effect, if any in humans. This view is also supported by the fact that fructosan- and oligosaccharide-based food ingredients having no viscosity-elevating effect but acting as substrates in colon fermentations have in most studies had no or only minor cholesterol-reducing effects.

B. Hypoglycemic Effects

Diets giving a slow postprandial release of glucose and insulin have been studied and practiced actively since the late 1970s. The importance of viscosity was shown in experiments with guar gum, hydrolyzed guar gum, and other thickeners or fiber sources (84). In one case study from 1980 (36), a daily intake of a coarse oat fraction enabled a diabetic patient to reduce his insulin intake to zero while keeping his serum glucose in a normal range. Compared to many other foods, oats have a low postprandial glycemic response (85). In vitro studies with rat small intestine rings (81) have shown that oat gum retards monosaccharide uptake due to the increased viscosity and its effect on the reduction of diffusion and due to the thickness of the so-called unstirred layer on the absorption site.

In glucose tolerance tests, doses of 1.8, 7.2, and 14.5 g of β-glucan have effected reductions in the peak glucose value of 17, 40, and 60%, respectively (59,86). The relationship of increment in peak plasma glucose and peak plasma insulin to viscosity was the same as for guar gum (59).

Effects of β-glucan from oat gum and from oat bran as ingredients in meals have been studied with both healthy and type 2 diabetic (NIDDM) subjects (87) with doses of 8.8 g of β-glucan per meal. In healthy control subjects, glucose excursions (differences between the highest and lowest glucose levels) were 43 or 38% lower with oat gum or oat bran than with control meal, and the 3-hour areas under the curve above baseline were 28.5 or 27.2% lower, respectively, than with controls. With type 2 diabetic subjects, the levels of excursions were higher and the duration longer than with healthy subjects, and with the oat gum and oat bran meals the glucose excursions were 27.4 or 33.9% lower, respectively, than those of controls. Changes in insulin followed the same pattern.

In a study with NIDDM patients (88), β-glucan deriving from an ethanol wet-milled oat bran concentrate was incorporated in a cooked extruded breakfast cereal. With doses of 4.0, 6.0, or 8.4 g of β-glucan per meal, peak elevations of glucose were reduced by 33, 59, or 62%, respectively, from the control meal values, and 4-hour areas under curve above basal values by 29, 39, and 65%, respectively, from the control. Peak insulin values were reduced by 33, 38, or 41%, respectively. The higher responses compared to those of the previous study (87) might be due to differences in the solubility of β-glucan.

In a long-term study (68), eight men with NIDDM received in bread products for 12 weeks 9 g of β-glucan per day originating from ethanol wet-milled oat bran concentrate. The total carbohydrate level of the diet was 55%. During the oat bran concentrate period, total glucose response area was reduced by 46% ($p \leq 0.05$) and total insulin response area by 19% (not significantly). The glucose peak values after breakfast and lunch decreased by 15 and 25%, respectively.

There has also been interest in applying the hypoglycemic effect of oat soluble fiber to improving performance in sports. In a comparison of the effects of corn, wheat, and oat cereals on the respiratory quotient and on blood glucose, insulin, and amino acids at rest and during exercise (89), oat cereal gave the lowest glucose and insulin values for 90 minutes after the meal. After the first 20 minutes of exercise the glucose level was higher than with corn or wheat, but subsequently the differences were small, and no difference was observed in performance. The amount of β-glucan obtained from the oat cereal was, however, only approximately 1.1 g, and in view of the results of diabetic studies, more favorable effects would have been expected with higher doses.

The above results indicate that an effective dose for reducing postprandial elevations of glucose and insulin is about 6 g per meal provided that it is prehydrated or in an easily hydratable state and that its macromolecules have not been degraded.

C. Gastrointestinal Effects

Both soluble and insoluble oat fiber have gastrointestinal effects—soluble fiber mainly due to its high swelling and water-binding ability and as a substrate of colon fermentations, and insoluble fiber mainly due to its bulking effect.

Data on the effect of oat fiber on stomach emptying are controversial. The high swelling and water-binding properties of oat soluble fiber would lead one to expect delayed stomach emptying. Using radioactivity counting it was found (90) that an amount of 9 g of total dietary fiber per meal from oat bran caused no difference in the emptying rate as compared to semolina porridge control. In studies with pigs, use of relatively larger amounts of oat bran has been possible, and a viscosity-related delaying effect has been observed (91,92). A dose of 16 g of β-glucan from oat flour per kg dry matter of feed, elevating the viscosity of the liquid fraction in the stomach to approximately 15 mPa·s at a shear rate of 45 s^{-1}, caused an increased retention of liquid and solid markers, of digesta and of dry matter.

In the small intestine of humans, β-glucan remains intact, since no mammalian enzymes are capable of hydrolyzing it. In pigs, the molecular weight of β-glucan decreases, especially in the distal end, due to the effect of bacterial enzymes (92). Due to physical barriers to hydration and enzymatic action, intact remnants of the plant tissue are still observed, and the individual variations in viscosity ranged from 2 to 195 mPa·s, with the highest mean value (90 mPa·s) in the distal third of the small intestine 3 hours postprandial (92). In human ileal effluents (93), 88.5% of the β-glucan ingested was recovered.

Published clinical studies (Table 2) and animal studies (96) show that oat soluble fiber increases the fecal wet weight and reduces total transit time. Because β-glucan as such decomposes in the large intestine, the increase in dry weight is caused mainly by an increase in microbial cells, as shown in animal studies (97). The microbial cell material also retains more water than insoluble fiber, which increases the water content of the stool. Like other fiber sources that act as substrates for fermentation in the large intestine, oat soluble fiber can cause evolution of gas, especially when the amount ingested in the diet is changed suddenly. Compared to wheat bran, oat bran is reported to induce less discomfort and less formation of hydrogen and methane (94). Individual variations in the evolution of gas are large, but on average the amount of hydrogen produced from isolated oat gum, uncooked oats, or cooked oats is 58, 91, or 68%, respectively, of the amount produced from lactulose (98). Oat soluble fiber also causes a reduction in stool pH (97).

Insoluble oat fiber from oat hulls also increases the wet and dry weight of feces, but relatively less than oat soluble fiber. Oat hull fiber is not fermented in the large intestine (46).

D. Other Effects

In diets for weight reduction, oat soluble and insoluble fibers can act as water-binding and fat-mimicking ingredients. As stated earlier, oat fiber also increases the excretion of fat through the feces. An important function is its often reported effect on the feeling of satiety, probably caused by several simultaneous mechanisms.

In the large intestine, β-glucan is completely decomposed by bacterial enzymes and acts as a substrate for fermentations similar to other sources of soluble fiber. The physiological effects of these fermentations are described in other chapters of this book. The most important of these are probably the reduction of risk of intestinal and other cancers, effects on satiety, renal nitrogen load reduction, and prebiotic function.

In regard to the reduction of cancer risk, a special advantage of oat fiber is its lignan and

Table 2 Effect of Oat Soluble and Insoluble Fiber on Colon Function[a]

Preparation	Subjects no., sex, age	Insol. fiber (g/d)	Sol. fiber (g/d)	Fecal wet weight (g/d)	Fecal dry weight (g/d)	Transit time (h)	Stool frequency/day	Ref.
Control	6 f 65–73 yr			57.0	13.7		1.4	94
Oat bran		3	3	124.6	31.1		1.8	
Wheat bran		9.1	0.45	205.4	38.3		3.4	
Oat gum			7.5	73.1	22.0		1.8	
Raffinose			7.5	73.9	14.3		3.0	
Control	10 m 39–66 yr			134	27			79
Oat bran		8	8	191	42			
Control	6 m 4 f 24–36 yr			114	29	36		77
Rolled oats		5	5	125	34	30		
Control	8 m 35–62 yr			147	34.9			78
Oat bran		8	8	169	42.6			
Control	9 m 19–27 yr	15.5	2.7	85.3	24.6	73.1	0.68	95
Wheat bran		26.0	2.8	135.6	37.7	62.5	0.9	
Control		10.3	3.3	110.7	29.4	62.6	0.88	
Oat bran		18.8	9.1	156.4	42.4	53.0	0.92	
Control	10 m 20–37 yr			113	22.2	44.3		46
Oat hull fiber		17		155	45	42.0		

[a] Amounts fiber recalculated.

isoflavone content. These phytoestrogens are converted by intestinal bacteria to biologically active substances (for review, see Ref. 99). Over the long term these compounds probably reduce risks of mammary, prostate, and colon cancer. Reported total content of these compounds in oat bran varies from 2 to 7 mg/kg (100,101). The principal lignan components of oat bran are matairesinol and secoisolariciresinol, which are converted during intestinal fermentation to enterolactone and enterodiol. The level of lignans in oat bran is similar or higher than in rye, and in a dry enrichment of β-glucan content it is enriched in the same proportion. (H. Adlercreutz, unpublished).

One effect of oat soluble fiber seldom mentioned but having potential therapeutic value is an increase in the excretion of nitrogen through feces. This is a result of the increase in the microbial cell mass excreted and has been shown in pigs to elevate the amount protein excreted through feces fourfold compared to wheat flour (97,102). Increased fecal nitrogen excretion reduces correspondingly the urinary excretion and renal nitrogen load (103).

E. Effect of Processing and Storage on Physiological Efficiency

As stated above, the main effects of β-glucan depend on its viscosity. Processes that improve extractability of oat β-glucan thus increase its physiological efficiency, provided the macromolecules are not degraded in the process enzymatically or by shear forces, as stated above in connection with physical properties. Processing or storage conditions that lead to diminution of the extractability, such as formation of a glassy state or physical barriers for solubility in drying or semi-dry heat treatments or frozen storage (43), are expected to affect the physiological efficiency correspondingly.

VIII. SAFETY

Both oat meal and oat bran are generally recognized as safe (GRAS) under Sec. 170.30 (d) (21 CFR 170.30 (d)) (62). Oat gum has received GRAS status for specified uses; the applications listed include several types of cheese spreads, vegetables, meats, and frozen desserts, and no information on the possible carcinogenity or mutagenicity of oat gum is known (104). Use of oat hull fiber is permitted in the United States.

Some concern has arisen regarding reduced mineral absorption in connection with high intakes of dietary fiber. This is a problem common to several dietary fiber sources. Some minor components, especially phenolic compounds and phytic acid, accompanying fiber-rich plant tissues can bind divalent metal ions. Physiologically the most noticeable of these is binding of zinc and iron. In a long-term study with rats (105) absorption was affected by the level of the total mineral in the diet and not by the kind of fiber source. Diet did not appreciably affect mineral levels in soft tissues and bone. Nonheated oat bran reduces calcium availability and impairs absorption of mineral calcium (106). Magnesium absorption and retention as percent of intake are reduced, but the reduction is offset by the magnesium output from oat bran (106). Absorption and retention of iron, zinc, and phosphorus are increased (106). Ingestion of baked oat bran results in lower calcium and iron availability but has no effect on zinc, phosphorus, or magnesium absorption (106). Since fiber ingredients form only a minor part of the human diet, it is commonly suggested that these effects are easily compensated for by intakes from other food sources and might only in extreme cases result in low levels of zinc. In contrast, the complexing of iron by phytate and phenolic substances might be beneficial due to reduced fat peroxidation and formation of free radicals.

In animal studies where lipotropic substances—usually cholesterol and cholic acid—are added to feed to induce a hypercholesterolemic condition, infiltration of fat in the liver indepen-

dent of addition of insoluble or soluble fiber has been reported (21,107). With increasing amounts of β-glucan in the diet, the changes in the liver become more severe, but lipid infiltration into the liver occurs only when lipotropic substances are added to the feed (108).

In some earlier data residues of oat hulls were regarded as a health risk due to sharp silica crystals on their outer surface and their potential to cause internal bleeding. With present hulling technologies the amount of such residues has been reduced to less than one piece per serving (one ounce), and the problem is presently regarded to be nonexistent.

Oat is in general relatively free of agrochemical residues due to the fact that in cultivation the need for such chemicals is smaller than for other crops. Important chemical contaminants include fungal toxins.

A physical risk common to all easily hydratable polysaccharides exists for oat gum as well. If ingested in tablet form, rapid swelling and adhesive action might cause blockage of the upper digestive tract. At least one fatal case of esophagus blockage by a glucomannan preparation is known. The risk can be avoided by incorporating the fiber in food items or administrating it in powder or granular form accompanied by a large amount of water.

IX. FOOD APPLICATIONS

Up to now oat fiber applications have been almost completely limited to traditional cereal products, such as hot and cold breakfast cereals, breads, biscuits, snacks, and pasta products. However, there is no reason for this limitation. Possible other product groups include meat products, ready-to-eat meals, drinks or drink powders, dairy products, and desserts. Persons who want to increase their daily intake of soluble dietary fiber need a variety of choices of palatable food items to continuously maintain a diet rich in soluble fiber. Attention should, however, be paid not only to the minimal amount of β-glucan. To achieve the health effects desired, it is even more important that the β-glucan in the preparation has solubility and viscosity properties adequate for the end use. To maintain good compliance, sensory properties are a key factor. It is a challenge for the food industry to provide consumers of both conventional foods and dietetic foods with such variety.

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Review

Oat Products and Lipid Lowering

A Meta-analysis

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Objectives.—To test the a priori hypothesis that consumption of oats will lower the blood total cholesterol level and to assess modifiers and confounders of this association.

Data Sources.—A computerized literature (MEDLINE) search and the Quaker Oats Co identified published and unpublished trials as of March 1991. Raw data were requested for all trials.

Study Selection.—Trials were included in summary effect size estimates if they were randomized and controlled, if a formal assessment of diet and body weight changes occurred, and, if raw data were not received, if there was enough information in the published report to perform calculations.

Data Synthesis.—Twenty trials were identified. Using the methods of DerSimonian and Laird, a summary effect size for change in blood total cholesterol level of −0.13 mmol/L (−5.9 mg/dL) (95% confidence interval [CI], −0.19 to −0.017 mmol/L [−8.4 to −3.3 mg/dL]) was calculated for the 10 trials meeting the inclusion criteria. The summary effect size for trials using wheat control groups was −0.11 mmol/L (−4.4 mg/dL) (95% CI, −0.21 to −0.01 mmol/L [−8.3 to −0.38 mg/dL]). Calculation of Keys scores demonstrated that substituting carbohydrates for dietary fats and cholesterol did not account for the majority of blood cholesterol reduction. Larger reductions were seen in trials in which subjects had initially higher blood cholesterol levels (≥5.9 mmol/L [≥229 mg/dL]), particularly when a dose of 3 g or more of soluble fiber was employed.

Conclusion.—This analysis supports the hypothesis that incorporating oat products into the diet causes a modest reduction in blood cholesterol level.

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IN 1963, DeGroot and colleagues[1] were the first to report that the addition of an oat product to the diet of humans resulted in lowered blood cholesterol levels. In that trial, 21 male volunteers substituted for the usual bread in their diet bread containing 140 g of oatmeal. At the end of 3 weeks, the blood total cholesterol level was reduced 11%. Since that time a substantial amount of research has accumulated; both metabolic ward studies and trials of free-living subjects have been conducted in an attempt to determine whether oats do have an effect on blood lipid levels.

Anderson and colleagues[2-5] have published the results of several uncontrolled metabolic ward trials and have demonstrated total cholesterol reductions from 13% to 26%. They have also published a controlled metabolic ward study comparing oat bran with wheat bran and demonstrated a net total cholesterol reduction of 9% for the oat bran group.[6] Although many metabolic ward studies have shown rather impressive lipid reductions,[1,3,6] trials of free-living subjects have reported considerably more variability in lipid response.[7-23] A few have demonstrated virtually no benefit,[12,13] while others have shown reductions greater than 10%.[11]

At least some of the variability can be accounted for by differences in study subjects and protocols. Various oat preparations have been used, including cereals, muffins, breads, and entrees. Some trials have employed oat bran as the intervention while others have used oatmeal, and doses have differed from trial to trial. Some have enrolled an all-male cohort of subjects and others have used various combinations of younger and older men and women. The initial serum cholesterol level of subjects also has varied from trial to trial, with some including normocholesterolemic subjects and others enrolling only those with hypercholesterolemia. With all of the differences between trials, it is difficult, by qualitative inspection alone, to sift through the information and understand the factors that might account for the variability of the serum lipid response to oats.

In a recent oat bran trial completed by Keenan et al,[10] post hoc analysis of the data revealed that subjects' lipid responses appeared to vary by age and gender. Young women had virtually no response to oat bran, while older women showed a marked drop in cholesterol level (−0.37 mmol/L [−14.5 mg/dL]); younger and older men had intermediate responses. It is known that lipid levels differ according to gender and menopausal status, and there is evidence that suggests that bowel transit times differ according to gender and menopausal status as well.[24] In addition, at least three oat product trials have demonstrated a relation-

ship between the initial blood cholesterol levels of subjects and subsequent reduction in cholesterol level attributed to the oat product.[8-10] Therefore, it is plausible to suggest that age and gender as well as initial cholesterol level could be playing a role in the variability of lipid response. This meta-analysis formally summarizes the oat product literature of clinical trials of free-living subjects, with attention to whether blood cholesterol response varies by age, gender, dose and/or initial blood cholesterol level.

METHODS

Design of the Meta-analysis

A computerized literature (MEDLINE) search was conducted to identify all published oat product trials as of March 1991. In addition, a list of all known investigators of the lipid-oats association (regardless of funding source) was supplied by the Quaker Oats Co (Barrington, Ill). From this list unpublished trials were solicited and, when possible, included to maximize the database and reduce the possibility of publication bias. Letters were sent to all investigators, describing the proposal and inviting collaboration in the effort. Collaborators were requested to provide certain aspects of their raw data (lipid values, some dietary variables, body weight, age, and gender) as well as thorough descriptions of their study protocols. The response was very positive; of the 20 trials initially identified (12 published, five abstracts, three unpublished), raw data were received for 14 trials, for a response rate of 70%. For one of the three unpublished trials, no information could be obtained and the investigator declined to collaborate, so 19 trials were reviewed for this meta-analysis. The following are the a priori hypotheses:

- Oat products act as a lipid-lowering agent in human subjects, reducing the blood total cholesterol level and its low-density lipoprotein (LDL) component.
- A dose-response relationship exists between the amount of oat product consumed and the degree to which blood lipid levels are reduced.
- Subjects with high initial total cholesterol levels will demonstrate greater reductions in total cholesterol levels than will those with lower initial total cholesterol levels.
- The variables age and gender modify the response of total cholesterol levels—older women will demonstrate a greater reduction than all other age-gender subgroups.

It was necessary to receive the raw data from each trial to test the last hypothesis, since most published reports did not provide an age-gender breakdown of results. In oat product trials that measured changes in lipoprotein fractions, LDL was the fraction of total cholesterol shown to be most affected by oat products; changes in high-density lipoprotein and triglyceride levels were minimal or absent.[7-12,23,25] Although LDL would be the preferred lipid variable for use in determining intervention effects, not all the trials measured LDL levels; therefore, the total cholesterol level was used as the lipid variable of primary interest.

All 19 trials were reviewed and summarized. However, to be included in the primary calculation of the summary effect size, trials needed to meet the following a priori criteria:

- Trials had to have been controlled and randomized. Without a control group, there is no way to estimate any change in blood lipid levels that is occurring independent of the effect of the intervention.
- If a comparison product was used, it had to have been one with very low or no soluble fiber (eg, wheat bran).
- If a trial tested the intervention against a special background diet (eg, a low-fat, low-cholesterol diet), there had to have been a sufficient lead-in period (a minimum of 4 weeks for change to a low-fat, low-cholesterol diet[26]) so that the effects of the special diet on the change in blood lipid levels during the oat product intervention could reasonably be assumed to be negligible.
- All trials had to have made a formal assessment of dietary behavior and body weight changes in treated and control subjects.
- If investigators did not submit their raw data for analysis, the published report had to have an adequate description of design and the necessary information to calculate the appropriate effect size and associated SE.
- Crossover trials were analyzed in the primary analysis as parallel design trials when the raw data were available, using the information from just the first phase. This was done to avoid any problems with order effects (ie, group-by-phase interaction).

Because these criteria are somewhat subjective, the summary effect size was recalculated in several ways that allowed for the inclusion of trials without a lead-in diet phase and for including the results (by pooling) from both phases of crossover trials. The results were then compared.

To determine whether using the results of one treatment group to create multiple effect sizes by comparison with multiple control groups (from the same trial) had artificially decreased the amount of heterogeneity of the assembled effect sizes, the summary effect size was calculated using the information from multiple comparisons and then again after eliminating duplicate use of the same treatment group from Keenan et al (excluding the American Heart Association step 1 [AHA-1] diet-only comparison),[10] Beling (unpublished results, 1991, excluding the comparison with the no-diet group), and O'Brien et al (excluding the special diet only comparison),[18] and the results were compared.

When sufficient dietary data were included in the published report, Keys scores were calculated to determine whether the reduction in total cholesterol level could be attributed to dietary changes other than the inclusion of oats in the diet. Keys scores are calculated using the changes in saturated fatty acids, polyunsaturated fatty acids, dietary cholesterol, and energy intake to determine whether the diet has changed from preintervention to postintervention and to determine the degree to which any dietary change could have affected the blood total cholesterol level.[26,27] For the subset of trials for which Keys scores could be calculated, an adjusted individual effect size was computed for each trial by subtracting expected (estimated by Keys scores) from observed reductions in the total cholesterol level. A new summary effect size was then calculated by substituting the adjusted individual effect sizes into the DerSimonian and Laird[28] calculations described below.

The preliminary cholesterol level is the mean total cholesterol level in the oat-treated group just prior to the intervention phase. For trials in which a lead-in diet period preceded the intervention phase, the preliminary total cholesterol level is the value at the end of the lead-in period.

Soluble fiber (in grams) is used as the variable to represent dose when evaluating the existence of a dose-response relationship between oats and lipid reduction.

To assess the presence of age-gender interaction, only those trials that had enrolled subjects of both older and younger ages as well as men and women are included. The dichotomous age variable (<50 vs ≥ 50 years) is constructed as in the oat product trial that reported the age-gender interaction.[10] As such, it is a surrogate variable for menopausal status in women. Individual effect sizes are created for each age-gender subgroup within a trial (ie, each trial yielded four effect sizes), and linear regression methods were used to determine whether age and gender or their interaction could predict effect size. As a second look at the age-gender hypothesis, individual regression models were run on each trial for which raw data were available.

Statistical Methods

To calculate the net mean change in total cholesterol level (individual study ef-

fect size) during the intervention phase of each trial, the mean change in total cholesterol level for the control subjects was subtracted from the mean change for the treated subjects. A negative effect size indicates a reduction during the intervention phase. The variance was calculated as follows:

$$V(ES)=s^2[(1/n_{treated})+(1/n_{control})],$$

where V is the variance of the effect size (ES); s, the pooled SD of the change in total cholesterol level for the treated and control groups; and n, the sample size.

DerSimonian and Laird[28,29] proposed a method for calculating the summary effect size of trials assembled for a meta-analysis, and their technique was used here. Briefly, the assumption underlying their technique is that the estimates of treatment effect (individual effect sizes) are normally distributed. The null hypothesis of a lack of heterogeneity (assessed by the use of a χ^2 distribution) tests whether the variability between the effect sizes exceeds the variability within each effect size. This method allows for the creation of a correction factor (to be incorporated into the SE) that reflects the degree of heterogeneity between the effect sizes. As heterogeneity increases, the corrected SE increases and, consequently, confidence intervals (CIs) constructed about the final summary effect size widen. Correction for heterogeneity is made whether or not the χ^2 value for heterogeneity is statistically significant.

Linear regression analyses were performed using the general linear models (GLM) procedure of the SAS program.[30] The dependent variable is the individual effect size in millimoles per liter, and all models are weighted using the inverse of the variance of each effect size. This method is analogous to that of DerSimonian and Laird,[28] except that it is possible for the variance correction factor to be negative using linear regression methods.

RESULTS

Qualitative Review

Trials Excluded From the Summary Effect Size Calculations.—Table 1 describes trials that were not included in the calculation of the summary effect size. In all, seven trials were excluded completely. Four of these (F.W.T., unpublished results, 1991)[14,17,19] did not employ control subjects with respect to the oat product. In the trial of Thye, controls were used, but this trial tested a combination of exercise and oat products against exercise and no oat products, so the controls were deemed inadequate for the meta-analysis. In the trial of Hegsted et al,[17] rice bran and oat bran were tested independently; no other control was used.

Table 1.—Trials Not Included in Summary Effect Size Estimates

Source, y	No. of Subjects	Intervention*	Results†	Reason for Exclusion
O'Kell and Duston,[13] 1983	45	Dry, uncooked oats: ½ cup for men, ⅓ cup for women	No significant difference between "on oats" and "off oats" periods	No final mean values given, final No. of subjects not given; no discussion of statistical methods; no diet or body weight data provided
Hegsted et al,[17]‡ 1989	11	OB, 100 g; RB, 100 g	OB and RB each lowered cholesterol level by 7%	No normal diet control; only comparisons were between OB and RB
Storch et al,[18] 1984	12	OB, 53 g; WB, 53 g	Authors claim a 12% reduction in total cholesterol level; after correction for control group's change, net decrease was 7%	Abstract only; insufficient data to calculate effect size
Welch et al,[19] 1990‡	12	OB, 90 g	Mean change, −0.40 mmol/L (−16 mg/dL); significantly different from baseline	Uncontrolled
Stewart and Welch,[14] 1990‡	15	OM, 78 g	Mean change, −0.10 mmol/L (−4 mg/dL); not significantly different from baseline	Uncontrolled
Thye, 1991§‡	12	OB, 100 g	−0.27 ± 0.51 mmol/L (−10 ± 20 mg/dL)	No control group for oat products; the exercise intervention was controlled
	10	OM, 100 g	−0.66 ± 0.46 mmol/L (−26 ± 18 mg/dL)	
Reynolds et al,[20] 1989	43	84 g of cereal containing 24 g of OB; 84 g of corn flakes	Net change, −0.26 mmol/L (−10 mg/dL)	Abstract only; insufficient data to calculate effect size

*OB indicates oat bran, RB, rice bran; WB, wheat bran; and OM, oatmeal.
†These results are changes demonstrated by treated subjects; they do not take into account changes in control subjects, since these trials are either uncontrolled or have not published enough information to calculate a net effect size.
‡Raw data were received.
§Unpublished results.

Three other trials[13,18,20] were excluded because there was inadequate information available in the published report to calculate an individual effect size. The trials of Storch et al[18] and Reynolds et al[20] otherwise met the inclusion criteria. The trial of O'Kell and Duston[13] did not indicate that any formal diet or body weight assessment was performed, so it is questionable whether this trial would have been used even if sufficient information had been available.

Two additional trials, included at the bottom of Table 2 (Demark-Wahnefried et al[15] and O'Brien et al[16]), did not meet the more rigorous criteria but met the broadened criteria. Consequently, they were excluded from the first summary effect size calculation, when the a priori criteria were rigorously enforced, and included in a second calculation, when the broadened criteria were used.

Trials Included in the Summary Effect Size Calculations.—Table 2 describes the trials included in the calculation of the summary effect size. A total of 10 trials (S.B., unpublished results, 1991)[7-12,21-23] met the a priori inclusion criteria: they generated 19 individual effect sizes because some single trials included multiple treatment groups. When the trials of Demark-Wahnefried et al[15] and O'Brien et al[16] were included, 22 individual effect sizes were available for the summary effect size calculation. Subjects ranged in age from 20 to 73 years old. Eight trials utilized a parallel design (S.B., unpublished results, 1991),[7,9,11,15,21,23] three used a 2×2 oat bran and wheat bran crossover design,[10,12,22] and one used a 3×3 design[22] that tested oat bran, rice bran, and wheat bran. Two trials measured changes in apolipoprotein A-I and B levels in addition to measuring changes in total cholesterol and LDL levels.[22,23] The duration of treatment phases ranged from 18 days to 12 weeks, and 10 to 137 subjects were enrolled in each treatment or control group. The majority of the trials assessed diet by use of a 3- or 4-day written food record.

Quantitative Analysis

Calculation of the Summary Effect Size.—The first calculations yielded a summary effect size of −0.15 mmol/L (−5.9 mg/dL) (SE, 0.03 mmol/L [1.3 mg/dL]) with a 95% CI of −0.22 to −0.09 mmol/L (−8.4 to −3.3 mg/dL). The heterogeneity of the assembled effect sizes was not statistically significant (χ^2=26.5, P=.10).

When the broadened inclusion criteria were employed, all trials in Table 2 were included, and the results from the second phases of the crossover trials of Keenan et al[10] and Turnbull and Leeds[23,25] were also included (the diet-only comparison of the trial of Keenan et al[10] was excluded, so this was analyzed strictly as a crossover trial). The summary effect size (for the 22 individual effect sizes) was −0.13 mmol/L (−5.1 mg/dL) (SE, 0.03 mmol/L

Table 2.—Trials Included in the

Source, y	Study Design	Younger Men/Older Men/ Younger Women/ Older Women, %†	Background Diet	Intervention‡ (No. of Subjects)
Van Horn et al,[7] 1986**	Parallel, 6-wk phase	33/17/35/15	AHA-1, 6-wk lead-in	AHA-1 + OB, 57 g (69)[a]
				AHA-1 + OM, 57 g (69)[b]
				AHA-1 diet only (70)
Van Horn et al,[8] 1988**	Parallel, 6-wk phase	33/4/43/20	AHA-1, 4-wk lead-in	AHA-1 + OM, 57 g (113)[c]; AHA-1 diet only (123)
Van Horn et al,[9] 1991**	Parallel, 8-wk phase	33/17/33/17	Usual	OM, 57 g (42)[c]; control (38)
Davidson et al,[11] 1991**	Parallel, 6-wk phase, 6 wk follow up	27/32/9/32	AHA-1, 8-wk lead-in	AHA-1 + OB, 28 g (23)[a]
		19/52/10/19	AHA-1, 8-wk lead-in	AHA-1 + OB, 57 g (20)[f]
		14/41/9/36	AHA-1, 8-wk lead-in	AHA-1 + OB, 84 g (21)[g]
		30/10/15/45	AHA-1, 8-wk lead-in	AHA-1 + OM, 28 g (20)[i]
		19/48/5/29	AHA-1, 8-wk lead-in	AHA-1 + OM, 57 g (21)[j]
		25/20/25/30	AHA-1, 8-wk lead-in	AHA-1 + OM, 84 g (20)[k]
				AHA-1 + WB, 28 g (15)
Gold and Davidson,[21] 1988**	Parallel, 4-wk phase	50/0/50/0	Usual	OB, 34 g (19)[a]
				Half OB (17 g), half WB (17 g) (28)[l]
				WB, 34 g (25)
Keenan et al,[10] 1991**‖	Crossover with concurrent diet controls, 6-wk phases	35/32/12/21	AHA-1, 6-wk lead-in	AHA-1 + OB, 57 g, AHA-1 + WB, 57 g (75 [total for crossover])[m], AHA-1 diet only (67)[n]
Kestin et al,[22] 1990**††	3×3 crossover testing OB, RB, and WB; three 4-wk phases	67/33/0/0	Low fiber, 3-wk lead-in	OB, 95 g (8 [parallel])[o]; WB, 35 g (6 [parallel]), RB, 60 g (24 [total 3×3 design])
Turnbull and Leeds,[23,24] 1989 and 1987**††	Crossover; 4-wk phases	13/38/25/25	Low fat, 4-wk lead-in	Low fat + OM, 150 g[p], low fat + Wheatabix, 150 g (17 [total])
Swain et al,[12] 1990‡‡	Crossover, 6-wk phases, 2-wk washout	20/0/80/0	Usual, 1-wk control period	OB, 100 g[q]; WB, 100 g (20 [total])
Beling, 1991**§§	Parallel, 4-wk phase	43/29/13/16	AHA-1, 4-wk lead-in	AHA-1 + OB, 40 g (119), AHA-1 diet only (137)[r]; control (no diet, no OB) (91)[r]
Demark-Wahnefried et al,[15] 1990*‖‖¶¶	Parallel, 12-wk phase	36/18/20/26	LFLC *or* usual, no lead-in	LFLC only (15); LFLC + OB, 50 g (18)[s]; usual diet + OB, 50 g (15); usual diet + processed OB, 42.5 g (20)
O'Brien et al,[16] 1985‖‖	Parallel, 18-day phase	##	High complex carbohydrate, high fiber, 3-day lead-in	Special diet + OB, 50 g (15)[t]; special diet + WB, 50 g (15)[t]; special diet only (15)

*AHA-1 indicates American Heart Association step 1 diet; OB, oat bran; OM, oatmeal; WB, wheat bran; RB, rice bran; and LFLC, low fat, low cholesterol.
†Younger men and women are those less than 50 years of age; older men and women are those 50 years of age or older.
‡The superscript lowercase letters indicate correspondences with Fig 1.
§Soluble fiber values are *estimates* in many trials. The values from the Nutrition Coding Center of the University of Minnesota are 2 g of soluble fiber in 28 g of OB and 1 g of soluble fiber in 28 g of OM.
‖These values are the means of the cholesterol levels of oat-treated subjects after the lead-in diet phase and before the intervention phase.
¶These values are pooled SDs of the oat and control groups.
#Confidence intervals were constructed using the methods of DerSimonian and Laird.[26]

(1.12 mg/dL]) with a 95% CI of −0.19 to −0.07 mmol/L (−7.3 to −2.9 mg/dL). The heterogeneity of these effect size estimates was not statistically significant (χ^2=25.8, P=.20).

Keys Scores.—Table 3 provides Keys scores generated for the trials that had included diet data in published reports.[7-12,15] Using each arm of these trials as the unit of observation, the correlation between the observed change in total cholesterol level and the expected change as determined by Keys scores was .63 (P=.001).

The vast majority of the oat-treated groups demonstrated greater-than-predicted reductions in mean total cholesterol level. In the trial of Swain et al,[12] Keys scores for both the oat- and wheat-treated groups were almost identical; the observed reduction in total cholesterol level for the oat period was slightly less (0.05 mmol/L [1.9 mg/dL]) than predicted by Keys scores. In the trial of Davidson et al,[11] the 57-g oatmeal group demonstrated just a slight reduction in total cholesterol level beyond that predicted; this is an exception to the general trend demonstrated by the other five oat-treated groups in this trial that the reduction in total cholesterol level was far greater than predicted by the Keys scores.

For this subset[7,12,15] of 13 individual effect sizes for which Keys scores were calculated, the summary effect size before any adjustment for expected changes in total cholesterol level was −0.17 mmol/L (−6.5 mg/dL), with a 95% CI of −0.25 to −0.09 mmol/L (−3.5 to −9.7 mg/dL) and an SE of 0.04 mmol/L (1.6 mg/dL). The summary effect size after adjustment for expected changes in total cholesterol level (estimated by Keys scores) was −0.18 mmol/L (−6.8 mg/dL), with a 95% CI of −0.31 to −0.05 (−12 to −2 mg/dL) and an SE of 0.06 mmol/L (2.5 mg/dL). The χ^2 values for heterogeneity between the individual effect sizes were 10.8 and 46 before and after adjustment, respectively; the latter value indicates statistically significant between-effect size heterogeneity (P<.005).

Predictor Variables

The preliminary total cholesterol level for each trial was highly predictive of the subsequent reduction in total cholesterol level. R^2=0.46; the reduction in effect size per unit of preliminary total cholesterol was −0.14 (SE, 0.037, P=.001).

Neither age nor gender nor their interaction term demonstrated an ability to predict subsequent response to oats. The mean of the effect sizes for the four subgroups were: young men, −0.25±0.29 mmol/L (−9.8±11.2 mg/dL); older men,

Final Effect Size Estimate*

Estimated Soluble Fiber in Intervention, g§	Preintervention Mean Serum Cholesterol Level,‖ mmol/L (mg/dL)	Effect Size,¶ mmol/L (mg/dL)	95% Confidence Interval,# mmol/L (mg/dL)
4.1	5.1 (196)	−0.11 ± 0.45 (−4.2 ± 17.4)	−0.26 to 0.04 (−10.0 to 1.6)
2.2	5.0 (195)	−0.14 ± 0.43 (−5.3 ± 16.7)	−0.28 to 0.01 (−10.9 to 0.30)
2.2	5.0 (193)	0.08 ± 0.48 (−3.2 ± 18.4)	−0.20 to 0.04 (−7.9 to 1.5)
2.2	6.6 (254)	−0.32 ± 0.50 (−12.3 ± 19.5)	−0.55 to −0.09 (−21.2 to −3.5)
2.0	7.0 (269)	−0.25 ± 0.74 (−9.8 ± 28.7)	−0.79 to 0.28 (−30.5 to 10.9)
4.1	6.9 (266)	−0.70 ± 0.68 (−27.0 ± 26.2)	−1.2 to −0.22 (−45.6 to −8.5)
6.1	6.9 (265)	−0.51 ± 0.59 (−19.6 ± 22.8)	−0.87 to −0.14 (−33.6 to −5.6)
1.1	6.8 (264)	−0.29 ± 0.65 (−11.3 ± 25.0)	−0.73 to 0.15 (−28.3 to 5.7)
2.2	6.9 (265)	−0.23 ± 0.70 (−8.7 ± 27.1)	−0.73 to 0.28 (−28.1 to 10.7)
3.2	7.1 (275)	−0.56 ± 0.69 (−21.7 ± 26.8)	−1.1 to −0.06 (−41 to −2.4)
2.5	4.6 (179)	−0.25 ± 0.40 (−9.6 ± 15.6)	0.50 to 0.00 (−19.4 to 0.24)
1.2	4.7 (183)	+0.01 ± 0.47 (0.57 ± 18.12)	−0.24 to 0.28 (−9.5 to 10.8)
3.1	5.9 (229)	OB vs WB: −0.11 ± 0.54 (−4.2 ± 20.9); OB vs diet only: −0.32 ± 0.66 (−12.3 ± 25.7)	OB vs WB: −0.4 to 0.14 (−13.9 to 5.5); OB vs diet only: −0.59 to −0.04 (−23.0 to −1.5)
5.8	5.8 (223)	−0.27 ± 0.51 (−10.4 ± 19.7)	−0.86 to 0.32 (−33.1 to 12.2)
6.0	6.3 (243)	−0.29 ± 0.61 (−11.3 ± 23.6)	−0.92 to 0.34 (−35.7 to 13.2)
5.8	4.8 (186)	−0.03 ± 0.41 (−1 ± 15.9)	−0.21 to 0.18 (−8.0 to 7.0)
2.9	5.5 (212)	OB vs AHA-1: −0.09 ± 0.59 (−3.3 ± 22.7); OB vs no diet, no OB: 0.00 ± 0.52 (± 0.13 ± 20.2)	OB vs AHA-1: −0.23 to 0.06 (−8.9 to 2.3); OB vs no diet, no OB: −0.14 to 0.15 (−5.4 to 5.7)
3.6	7.2 (278)	LFLC vs LFLC + OB, 50 g: +0.21 ± 0.79 (± 8.3 ± 30.4); *uncontrolled changes*: LFLC, −1.2 (−46), LFLC + OB, 50 g: −1.1 (−41), usual diet + OB, 50 g: −0.92 (−35.6), usual diet + processed OB, 42.5 g: −0.73 (−28)	LFLC vs LFLC + OB, 50 g: −0.36 to 0.79 (−13.8 to 30.4)
7.6	7.1 (276)	OB vs WB: −0.28 ± 1.1 (−10.7 ± 41.7); OB vs diet only: −0.12 ± 0.82 (−4.5 ± 31.6)	OB vs WB: −1.1 to 0.53 (−41.9 to 20.5), OB vs diet only: −0.73 to 0.49 (−28.1 to 19.1)

**Raw data were received.
††These studies were analyzed as parallel-design trials; statistics in this table were calculated using parallel-design methods.
‡‡Raw data were not available; this study was analyzed as a crossover trial in all calculations. The authors stated that no group-by-phase interaction existed.
§§Unpublished results, 1991.
‖‖Data from these studies are included in the second of two summary effect sizes mentioned in the text (see the "Results" section for details).
¶¶Of the three treatment groups, the effect size could be calculated only for LFLC vs LFLC + OB, 50 g; the other two treatment groups did not have comparable control groups.
##One third of the subjects were women; no age breakdown was provided.

-0.31 ± 0.35 mmol/L (-12.0 ± 13.7 mg/dL); young women, -0.21 ± 0.44 mmol/L (-8.2 ± 17.2 mg/dL); and older women, -0.28 ± 0.28 mmol/L (-10.8 ± 11.0 mg/dL).

Davidson et al[11] recently performed a trial that tested a dose-response hypothesis. Because the raw data for the trial of Davidson et al[11] were available, a linear regression model was built with dose (grams of soluble fiber) and preliminary total cholesterol level as independent variables and change in total cholesterol level as the dependent variable. R^2=0.26; the reduction in effect size per unit of soluble fiber was −3.3 (SE, 1.07; P=.002), and the reduction in effect size per unit of preliminary total cholesterol was −0.36 (SE, 0.059; P<.0001).

To assess a dose-response relationship between individual effect sizes and the dose of soluble fiber for trials in the meta-analysis, linear regression methods were used to describe the interactive association of dose and preliminary total cholesterol level with effect size. With a dichotomous dose variable (<3 g vs ≥3g) and a continuous range of preliminary total cholesterol levels, the interaction term was statistically significant (P=<.05), and R^2=0.61. Table 4 shows mean effect sizes when the individual effect sizes are split into preliminary total cholesterol/dose subgroups. Trials that had the largest reduction in total cholesterol level were those whose subjects had the highest preliminary total cholesterol level and tested the higher doses. The association of the dose of the oat product and subsequent total cholesterol reduction appears to be blunted when initial cholesterol levels are low. There was considerable variability of the individual effect sizes even within the four subgroups suggested by the interaction.

COMMENT

Meta-analyses: Goals and Limitations

Meta-analyses are typically conducted to qualitatively describe the available research, compute a pooled estimate that reflects the available evidence, explain contradictory results between independent trials, and perform subgroup analyses that would not be possible within independent trials.[31,32] Two major criticisms have been leveled at meta-analyses. First, "file drawer" bias occurs when pooled estimates are derived solely from published reports and consequently may be a skewed representation of the entire body of research.[33,34] Second, assembled trials may be quite heterogeneous, in terms of both study design (ie, phase duration, subject selection, blood-drawing protocols) and the relative qual-

Table 3.—Energy Values, Keys Scores, and Body Weight Changes*

Source, y	Diet Assessment Tool	Intervention†	Energy Intake, kJ/d		Change in Total Cholesterol Level, mmol/L (mg/dL)		Change in Body Weight, kg
			Initial	Final	Predicted‡	Observed	
Van Horn et al,[7] 1986	3-Day food record	OB, 57 g	6896	6565	+0.13 (+5.1)	−0.14 (−5.4)	−0.27
		OM, 57 g	7384	7274	−0.07 (−2.7)	−0.17 (−6.5)	−0.27
		AHA-1 diet only	7514	7064	+0.08 (+2.9)	−0.03 (−1.2)	−0.41
Van Horn et al,[8] 1988	3-Day food record	OM, 57 g	6510	7039	−0.06 (−2.3)	−0.16 (−6.0)	+0.09
		AHA-1 diet only	6300	6422	0.00 (+0.11)	−0.07 (−2.8)	−0.27
Van Horn et al,[9] 1991	3-Day food record	OM, 57 g	8022	8341	−0.06 (−2.4)	−0.40 (−15.5)	−0.29
		AHA-1 diet only	8429	8488	+0.08 (+3.1)	−0.09 (−3.5)	+0.29
Keenan et al,[10] 1991	Baseline: FFQ; each phase: 4-day food record	OB-WB§	7602	7400	+0.01 (+0.27)	−0.15 (−5.8)	0
		WB-OB§	7804	7388	−0.01 (−0.42)	−0.11 (−4.3)	−0.4
		AHA-1 diet only	7972	7619	0.00 (+0.09)	+0.35 (+13.5)	−1.3
Swain et al,[12] 1990	Baseline: FFQ; each phase: 4-day food record	OB, 87 g	8673	10202	−0.41 (−15.8)	−0.36 (−13.9)	+0.3
		WB, 87 g	8673	9723	−0.39 (15.0)	−0.34 (−13.1)	+0.2
Davidson et al,[11] 1991	4-Day food record	OM, 28 g	5968	6140	−0.06 (−2.2)	−0.28 (−10.8)	−0.36
		OB, 28 g	6346	6644	+0.04 (+1.6)	−0.23 (−9.0)	−0.55
		OM, 57 g	5842	6560	−0.19 (−7.2)	−0.22 (−8.6)	−0.55
		OB, 57 g	7144	7321	−0.17 (−6.6)	−0.67 (−26.0)	−0.59
		OM, 84 g	6334	7253	−0.16 (−6.3)	−0.54 (−21.0)	+0.18
		OB, 84 g	6821	7493	−0.16 (−6.3)	−0.52 (−20.0)	−0.41
		WB, 28 g	5909	5788	0.00 (+0.01)	+0.02 (+0.77)	−1.0
Demark Wahnefried et al,[13] 1990	Daily food record	LFLC diet + OB, 50 g	9400	6833	−0.28 (−14.6)	−1.1 (−41.4)	−4.1
		OB, 50 g	8984	8102	−0.38 (−4.2)	−0.92 (−35.6)	−1.6
		OB, 42.5 g	9059	7753	−0.11 (−5.6)	−0.72 (−28.1)	0
		LFLC diet only	9253	6699	−0.14 (−10.8)	−1.2 (−46.0)	−3.0

*OB indicates oat bran; OM, oatmeal; AHA-1, American Heart Association step 1 diet; WB, wheat bran; LFLC, low fat, low cholesterol; and FFQ, food frequency questionnaire.
†See Table 2 for a more complete description of interventions.
‡Predicted changes were calculated using Keys scores: $\Delta C = 1.35\,(2\Delta S - P) + 1.5\Delta Z$, where C is the total blood cholesterol level, S, the percentage of kilocalories consisting of saturated fatty acids, P, the percentage of kilocalories consisting of polyunsaturated fatty acids; and $Z = \sqrt{\text{Dietary Cholesterol (milligrams)}/1000 \text{ kilocalories}}$.
§OB-WB indicates subjects who consumed OB in the first phase and WB in the second phase; WB-OB, subjects who consumed WB in the first phase and OB in the second phase.

ity of each trial.

In our meta-analysis, "file drawer" bias was minimized by actively soliciting research from all known investigators, regardless of whether the results had been published; the inclusion criteria set the minimum standard of quality. Additional variance caused by heterogeneity between the individual effect sizes was estimated by the methods of DerSimonian and Laird.[28] To determine whether heterogeneity had been artificially decreased by creating more than one individual effect size using one treatment group and multiple control group comparisons (ie, duplicating the use of a single treatment group result), the summary effect size was recalculated in the two ways done formerly (once with the a priori inclusion criteria enforced and once with broadened criteria), but removing any effect sizes that were generated as a result of the multiple use of treatment groups. Table 5 shows the results of the calculations and recalculations. It is clear by comparison that inclusion or exclusion of the duplicate information does not affect the summary effect size in any important way.

It could be argued that trials using wheat bran as a comparison are better controlled than trials incorporating oats isocalorically into the diet of treated subjects without providing a comparison product for controls. Table 5 displays the summary effect size calculations when trials are stratified according to this difference in design. Clearly, the stratified analysis supports the same conclusion as the unstratified one. For the stratified analysis, only the 28-g oat bran and 28-g oatmeal individual effect sizes were used from the trial of Davidson et al[11] (these treatments were comparable by weight to the control treatment of 28 g of wheat cereal), which reduced the magnitude of the summary effect size because the four excluded treatment groups had high initial cholesterol levels (average of 6.9 mmol/L [268 mg/dL]).

There is heterogeneity with respect to other aspects of study design, which is the case in virtually every meta-analysis. For example, the intervention phase durations of these trials ranged from 18 days to 3 months; investigators used a variety of recruitment methods to obtain their subjects, and the number of subjects in each trial differed widely. When this information is pooled, definitions necessarily broaden. Interpretations are valid, however, provided conclusions are drawn with the broadened definitions in mind: short-term intervention trials employing a dose of approximately 3 g of soluble fiber and enrolling primarily healthy middle-class men and women with the motivation and the resources to make dietary changes.

Summary Effect Size

Two potential confounders are changes in total cholesterol level attributable to regression toward the mean[25] and dietary changes known to affect lipid levels. Since uncontrolled trials were excluded from the summary effect size and the individual effect sizes were computed by adjusting for any change in total cholesterol level occurring in the control groups, regression toward the mean with respect to the summary effect size was not a confounder in this analysis. Regression toward the mean did not importantly confound with respect to initial cholesterol level as a predictor variable because, with two exceptions (S.B., unpublished data, 1991),[9] trials either did not recruit exclusively hypercholesterolemic subjects,[7,8,12,21] or, if they did, the initial cholesterol value was the mean of multiple measures.[10,11,22,25]

It has been suggested[12] that the reported lipid-lowering effect of oat prod-

Table 4.—Effect Sizes for Change in Total Cholesterol Level by Dose and Initial Cholesterol Level

Intervention Dose	Effect Size, mmol/L (mg/dL)*	
	Initial Cholesterol Level <5.9 mmol/L (<229 mg/dL)	Initial Cholesterol Level ≥5.9 mmol/L (≥229 mg/dL)
<3.0 g of soluble fiber from oats	−0.09 ± 0.10 (−3.4 ± 3.8)†	−0.27 ± 0.04 (−10.5 ± 1.6)‡
≥3 g of soluble fiber from oats	−0.13 ± 0.12 (−5.2 ± 4.8)§	−0.41 ± 0.21 (−16.0 ± 8.3)‖

*Values are mean ± SD.
†There were six effect sizes.
‡There were four effect sizes.
§There were three effect sizes.
‖There were six effect sizes

ucts is really the result of a substitution of carbohydrates for dietary fat and cholesterol. Keys and colleagues[26] studied men under metabolic ward conditions and developed the equation we used in which a change in blood total cholesterol level could be predicted by knowing the dietary changes in saturated fatty acids, polyunsaturated fatty acids, and cholesterol. Keys et al[26] and others[27] have tested the use of Keys scores in free-living subjects using diet records as their source of data, and they found that the predictive ability is still very good. Use of Keys scores is intended to measure group changes when components of a diet are being changed isocalorically; they are not intended for extrapolation to the individual subject, and both Keys et al[26] and more recent investigators[36] have demonstrated the variability of an individual's serum cholesterol response to dietary changes. Keys scores (Table 3) did not predict well in the trial of Demark-Wahnefried et al,[15] in which subjects reduced their energy intake and consequently lost weight in their attempts to adhere to the low-fat, low-cholesterol diet. In the trial of Swain et al,[12] energy consumption increased 1470 kJ/d during the treatment period, so the use of Keys scores may not have been entirely appropriate. The usefulness of Keys scores in this meta-analysis is limited to acting as a standard from which to judge whether reductions in total cholesterol level could be primarily attributed to the substitution of oats for dietary fats and cholesterol. The summary effect size calculated for a subset of trials after adjustments for changes in total cholesterol level due to substitution differed very little from the unadjusted summary effect size of this same subset of trials and very little from the unadjusted value of the entire sample of trials.

The trials of O'Brien et al[16] and Demark-Wahnefried et al[15] were originally excluded because there was not a sufficient lead-in period to ensure that the effects of the special diets (high-fiber, high–complex carbohydrate diet in the trial of O'Brien et al[16] and low-fat, low-cholesterol diet in the trial of Demark-Wahnefried et al[16]) on the change in blood lipid levels was negligible. However, any effect of a special diet should cancel out in randomized controlled trials when adjustments are made for the control group's change in total cholesterol level, so the two trials in question could be considered with the others. The summary effect size was calculated with and without the two trials in question, and it is clear that their inclusion did not increase the heterogeneity of the assembled individual effect sizes (χ^2 values were 25.8 and 26.5 for inclusion and exclusion, respectively).

The Figure illustrates why there appears to be such confusion about whether or not oats truly lower blood cholesterol levels. Apparently, many investigators overestimated the expected effect size when planning the sample sizes of trials, perhaps because outcomes were expected to mirror the results of early metabolic ward trials, in which total cholesterol changes as large as −0.75 mmol/L (−25 mg/dL) were reported[3,4,6]; consequently, power was lacking to detect a difference of 0.13 to 0.15 mmol/L (5 to 6 mg/dL).

By no means, however, has all of the variability in response between the trials been explained. The unpublished trial by Beling (1991) was the largest single trial that showed no significant reduction of total cholesterol level attributable to the oat product. The controls and treated subjects demonstrated significant reductions in total cholesterol levels during the lead-in diet period, but reductions beyond that point were slight. All of the groups demonstrated weight loss, from −1 to −2.7 kg. This trial and the trial of Demark-Wahnefried et al[15] were similar, in that both demonstrated weight loss, and the treated subjects in both failed to show significant reductions in total cholesterol levels compared with controls. This leads to speculation that the lipid reduction due to weight loss overshadows any contribution to reduction by oats and suggests that the effect of oats on blood lipid levels is best seen in weight-stable individuals. However, this ecologic observation has just two trials in evidence; more information is needed to draw any firm conclusions about a potential interaction of weight loss and oat product consumption on lipid reduction.

Age-Gender Interaction

As described previously, Keenan et al[30] reported a significant age-gender interaction and found that older women had the most marked total cholesterol reduction of the age-gender subgroups, but this observation was not supported in the meta-analysis. A major limitation of this retrospective subgroup analysis is that stratification did not occur for age and gender in any of these trials, so the randomization scheme could have been broken. Additionally, statistical power may have been insufficient to detect differences between subgroups since most trials had very few subjects in at least one of the subgroups. It is possible that a response in total cholesterol level modified by the interaction of age and gender could still be found in a trial specifically designed to test this hypothesis.

Initial Cholesterol Level

The finding that initial cholesterol level played an important predictive role in the outcome of the intervention was previously reported in three individual clinical trials.[8-10] The negative results of the highly publicized trial of Swain et al,[12] in which the mean preliminary total cholesterol level of the 20 subjects was just 4.8 mmol/L (186 mg/dL), are likely attributable to the low initial total cholesterol level of those subjects. In addition, the 9% reduction in total cholesterol level for the metabolic ward trial reported by Anderson et al[6] can be explained in part by the high initial cholesterol level of subjects (6.9 mmol/L [266 mg/dL]) and by the higher dose of oats employed (13.4 g of soluble fiber). The remaining difference may be attributable to differences in the ability to measure diet variables between free-living subjects whose diet is self-reported and subjects on metabolic wards whose diet is precisely measured and controlled.

Dose-Response

The determination of a dose-response relationship between oats and lipid lowering is difficult because the mechanism of action has continued to be elusive. The potential mechanisms have been thoroughly discussed,[2,37,38] and research continues in this area. For this analysis, grams of soluble fiber was chosen to represent the dose of the oat product because it is the best representation of β-glucan, the primary soluble fiber in oats. This measure, however, has limitations: The amount of soluble fiber obtained by measuring a quantity of oats will vary according to the solubilizing technique.[39] For the trials that did not directly measure the soluble fiber in their product, an estimate from the database

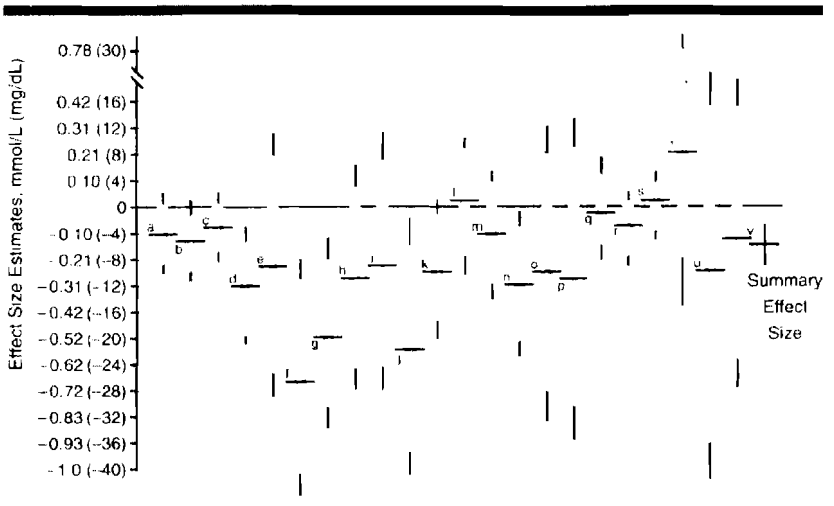
Table 5.—Description of Summary Effect Sizes Using Varying Inclusion Criteria

Inclusion Criteria*	Source	No. of Effect Sizes	χ^2	P†	Summary Effect Size, mmol/L (mg/dL)	95% Confidence Interval, mmol/L (mg/dL)
Trials using a priori criteria	Van Horn et al,[7,8] Keenan et al,[10] Davidson et al,[11] Swain et al,[12] Gold and Davidson,[21] Kestin et al,[22] Turnbull and Leeds,[23] Beling‡	19	26.5	.10	−0.15 (−5.9)	−0.22 to −0.09 (−8.4 to −3.3)
Trials using broadened criteria	Van Horn et al,[7,8] Keenan et al,[10] Davidson et al,[11] Swain et al,[12] Demark-Wahnefried et al,[15] O'Brien et al,[16] Gold and Davidson,[21] Kestin et al,[22] Turnbull and Leeds,[23] Beling‡	22	25.8	.20	−0.13 (−5.1)	−0.19 to −0.07 (−7.3 to −2.9)
Trials using a priori criteria but excluding the multiple use of treatment groups†	Van Horn et al,[7,8] Keenan et al,[10] Davidson et al,[11] Swain et al,[12] Gold and Davidson,[21] Kestin et al,[22] Turnbull and Leeds,[23] Beling‡§	17	21.3	.15	−0.16 (−6.1)	−0.22 to −0.09 (−8.7 to −3.5)
Trials using broadened criteria but excluding the multiple use of treatment groups†	Van Horn et al,[7,8] Keenan et al,[10]§ Davidson et al,[11] Swain et al,[12] Demark-Wahnefried et al,[15] O'Brien et al,[16]§ Gold and Davidson,[21] Kestin et al,[22] Turnbull and Leeds,[23] Beling‡§	19	22.7	.20	−0.14 (−5.6)	−0.20 to −0.09 (−7.9 to −3.3)
Trials using a priori criteria and stratifying by type of control subjects						
Control groups with wheat bran as a comparison product	Keenan et al,[10] Davidson et al,[11] Swain et al,[12] Gold and Davidson,[21] Kestin et al,[22] Turnbull and Leeds[23]	12	16.3	.20	−0.22 (−8.6)	−0.35 to −0.10 (−13.4 to −3.8)
Control groups with no comparison product	Van Horn et al,[7,8] Keenan et al,[10] Beling‡	7	8.5	.20	−0.11 (−4.4)	−0.18 to −0.04 (−7.1 to −1.7)

*See the text for descriptions of a priori and broadened criteria.
†Tests the null hypothesis that within-effect size variance is equal to between-effect size variance.
‡Unpublished results, 1991.
§One effect size only.

of the Nutrition Coding Center of the University of Minnesota, Minneapolis, was used, but this estimate could be somewhat imprecise because the amount of β-glucan may vary according to the variety of the oat as well as its growing environment.[40] This last point may help to explain at least some of the unexplained variability in total cholesterol response between trials. It is also possible that soluble fiber is an incomplete measure of dose; other components of oats as well as the way in which the oat product is prepared may play a role in the mechanism of action.[39]

There is the strong suggestion of a dose-response relationship between the amount of soluble fiber and the degree of lipid reduction, and there is significant evidence of an interaction between dose and initial cholesterol level with respect to total cholesterol reduction. Trials enrolling subjects with higher initial cholesterol levels (≥5.8 mmol/L [≥229 mg/dL]) and employing a dose of 3 or more g of soluble fiber demonstrated fivefold greater reductions in total cholesterol levels than trials whose subjects had lower initial cholesterol levels and that employed lower doses of fiber. This interaction is important when attempting to apply the results of this analysis to an individual. Three grams of soluble fiber is the equivalent of one large bowl of ready-to-eat oat bran cereal or three packets of instant oatmeal (oat bran has approximately twice the amount of soluble fiber as oatmeal). Thus, although individuals with high initial cholesterol levels would likely benefit from a single serving of oats, individuals whose blood cholesterol levels are already low may demonstrate little change in total cholesterol level by introducing a single serving of oats into their diet.



Effect size estimates. The summary effect size was calculated using a priori inclusion criteria. The lowercase letters near each effect size bar correspond to the effect sizes in Table 2. Shaded bars indicate 90% confidence intervals; solid line extensions, 95% confidence intervals.

Epidemiologic Aspects

The large number of subjects analyzed here does not automatically mean these findings can be extrapolated to the general population. These results are generalizable to people who resemble the study subjects—motivated adults who are able to make dietary changes.

In addition to its lipid-lowering benefits, research efforts are ongoing to determine whether dietary fiber can protect against certain forms of intestinal cancer.[37] It is feasible to project that the consumption of fiber is or will be on the rise as people look for healthy ways to alter their risk factor profiles. The potential side effects or disadvantages of fiber consumption then begin to take on more importance. There is evidence to suggest that components of dietary fiber, such as phytates and oxalates, can bind minerals in the gut (ie, zinc, calcium, iron, magnesium, phosphorus, and copper), decreasing their bioavailabil-

ity. The balance of the current research suggests that an increase in mineral excretion with fiber intake is not significant[37]; however, these trials are mostly short-term (usually 2 to 4 weeks) and are conducted with healthy adults. Special populations at risk of mineral deficiencies may need to be studied separately to determine whether major increase in fiber will increase this risk.

Ideally, a large-scale, long-term clinical trial (ie, 6 months or longer) should be conducted to verify the results of this review.

CONCLUSION

After careful consideration of the available evidence and investigation of potential confounders, this analysis provides strong support for the hypothesis that approximately 3 g per day of soluble fiber from oat products can lower the total cholesterol level 0.13 to 0.16 mmol/L (5 to 6 mg/dL) and that the reduction is greater in those with initially higher blood cholesterol levels. It is especially advantageous from a public health perspective that this modest reduction can occur by incorporating into the diet a food product with considerable nutritional value.

Modest reductions in blood cholesterol levels can have a dramatic impact when realized by large numbers of people. It has been estimated that a 1% reduction in the serum cholesterol level could reduce heart disease mortality in the United States by 2%.[41,42] Keeping in mind that oats and the dietary changes that accompany their incorporation may not be realistic for all people, if even the segment of the population at increased risk for cardiovascular disease were able to reduce its total cholesterol level 2% to 3%, this would have a very beneficial impact on rates of heart disease.

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CORRECTIONS

Errors in Table.—In the article entitled "Oat Products and Lipid Lowering," published in the June 24, 1992, issue of THE JOURNAL (1992;267:3317-3325), errors occurred in Table 5 on page 3224. The data in the fifth row across should have appeared as below. In addition, the footnote to Davidson et al, which was omitted, should have read as follows: "The 28-g oat bran and 28-g oatmeal effect sizes only."

Error in Figure.—An error occurred in the Diagnostic and Therapeutic Technology Assessment (DATTA) entitled "Surrogate Markers of Progressive HIV Disease," published in the June 3, 1992, issue of THE JOURNAL (1992;267:2948-2952). In the second panel (CD4 Ratio to Total T Cells) of the Figure on page 2949, the arrow should be over Promising, not Established.

Incorrect Statement.—In the Editorial entitled "Violence in America: A Public Health Emergency: Time to Bite the Bullet Back," published in the June 10, 1992, issue of THE JOURNAL (1992;267:3075-3076), the first bulleted item in the first full paragraph of the second column on page 3075 is incorrect and should be deleted.

Inclusion Criteria*	Source	No. of Effect Sizes	χ^2	P†	Summary Effect Size, mmol/L (mg/dL)	95% Confidence Interval, mmol/L (mg/dL)
Trials using a priori criteria and stratifying by type of control subjects						
Control groups with wheat bran as a comparison product	Keenan et al,[10] Davidson et al,[11] Swain et al,[12] Gold and Davidson,[13] Kestin et al,[14] Turnbull and Leeds[15]	8	4.6	.30	−0.11 (−4.4)	−0.21 to −0.01 (−8.3 to −0.4)

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Effect of β-Glucan from Oats and Yeast on Serum Lipids

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ABSTRACT: Heart disease is the leading cause of death in the U.S. One way to reduce the risk of developing the disease is to lower serum cholesterol levels by making dietary changes. In addition to reducing intake of total fat, saturated fat, and dietary cholesterol, serum cholesterol can be further reduced by added fiber, especially from sources rich in β-glucan. In this review, two sources of β-glucan are described; one source is oats and the other yeast. Their chemical structures and physical properties are compared, and their effect on serum lipid levels is described. Oat β-glucans are found in various breakfast cereals and snacks. Usually, several servings of these products are required to meet the Food and Drug Administration's claim of reducing the risk of heart disease. The yeast-derived fiber is a more concentrated source of β-glucan than the oat product. It is currently being tested in a wide variety of food products.

KEY WORDS: β-glucan, oats, serum lipids, cholesterol-lowering effect.

I. INTRODUCTION

Despite the decline in the incidence of and death from coronary heart disease (CHD) in recent decades,[1,2] CHD is still the leading cause of mortality and morbidity in the U.S. Approximately 700,000 patients in the U.S. are hospitalized each year with a diagnosis of acute myocardial infarction, and some 400,000 people die annually from CHD, which accounts for about one-third of all deaths.[3]

Few relationships in medicine are as well established as that between blood total cholesterol levels and the risk of developing CHD.[4] Numerous studies exist in which this association has been observed. The largest of these was based on the analyses of 356,222 men participating in the Multiple Risk Factor Intervention Trial (MRFIT).[5] The relative risk of mortality from CHD increased fourfold between the lowest serum cholesterol levels of less than or equal to 4.32 mmol/l (167 mg/dl) and the highest of greater than or equal to 6.83 mmol/l (264 mg/dl).[5]

A recent survey revealed that at least 25% of the adult US population have cholesterol concentrations above the desirable range (≥ 5.17 mmol/l [200 mg/dl]).[6] As a result, there has been a major public health effort to reduce serum cholesterol levels in these people.[7] Just a 1% reduction in serum cholesterol could reduce heart disease mortality by 2%;[8,9] thus, even

modest reductions could have a dramatic effect when generalized to the total hypercholesterolemic population.

Some individuals require drug therapy, while others could be managed by diet alone. Drugs are reserved for at-risk hypercholesterolemic patients who fail to achieve satisfactory cholesterol levels with a diet and exercise program. The most commonly prescribed drugs are the statins, which can be expected to reduce total cholesterol by 25%, decrease low-density lipoprotein-cholesterol (LDL-C) by 35%, and increase high-density lipoprotein-cholesterol (HDL-C) by 10% on average.[10] Dietary management includes the National Cholesterol Education Program (NCEP), which limits intake of total fat, saturated fat, and cholesterol.[7] Patients who adhere to the Step 2 version (greater reductions in saturated fat and cholesterol than in the Step 1 version) can expect a reduction in LDL-C of 15.6 to 18.9%. Other dietary modifications include increasing the intake of folate and vitamin B_6 through the diet and by supplements.[11,12] The relative risk of developing coronary artery disease as reflected in plasma homocysteine might be substantially reduced with intakes of folate of more than 2 1/2 to 3 times the Recommended Dietary Allowance and more than twice that of B_6.

In 1997, Hunick et al.,[13] using a computer simulation model based on an extensive literature review, examined whether changes in risk factors and in improved treatments account for the observed decline in CHD mortality in the U.S. The proportional contribution of these changes was also analyzed. Primary prevention (diet and drug therapy) accounted for one-fourth of the reduction in mortality. This includes lowering blood pressure, stopping smoking, and lowering serum cholesterol levels. Of that 25%, lipid-lowering alone accounted for one-third of the decline. By contrast, most of the decline in mortality (75%) was explained by improvements in the medical treatment given to these patients.

During the last few decades, several studies have indicated that diets high in complex carbohydrates, including starches and gumming (soluble) fibers, reduce serum lipid levels in hyperlipidemic individuals.[14-16] Soluble fibers include pectins, gums, mucilages, algal polysaccharides, and some hemicelluloses, which are found in legumes, oats, fruits, and psyllium. The purpose of this review is to compare the lipid-lowering effects of oats with those of a yeast-derived product. Oats were selected from the available soluble fiber-containing foods, because it is the grain, which is the most concentrated source of β-glucan; the yeast-derived product is also rich in it. First, we review the chemical aspects of β-glucans from oats and yeast and identify the lipid-lowering mechanism. Second, we provide a brief literature review of the effect of oat products on serum lipids in clinical trials. Third, we present the preliminary clinical data relating to the lipid-lowering effects of yeast-derived β-glucans.

II. β-GLUCANS

A. Oats

The component of oat-bran thought to be responsible for the lowering of cholesterol is its soluble, non-starch polysaccharide, β-glucan (Table 1). Oat meal (100 g) is 10.3% total dietary fiber, of which 5.2% is insoluble and 5.1% is soluble.[16] The soluble portion contains 4.2 g/100 g of β-glucan. Oat-bran is 15.9% total dietary fiber, of which 9.6% is insoluble and 6.3% is soluble. In 100 g, there are 6.8 g of β-glucan. Beta-glucan is a polysaccharide of a high molecular weight composed of β-(1→4)-linked glucose units separated every two to three units by a single β-(1→3)-linked glucose. It is a physiologically active gum that is unpalatable. Oat fiber disperses in water with difficulty, because it has a high viscosity and produces gel-like lumps even at a low concentration.

B. Yeast-Derived β-Glucan

Researchers at a U.S. biotechnology company[17] have developed a yeast-derived

TABLE 1
Comparison between Oat-Bran and Yeast-Derived β-Glucan

Component	Oat-bran	Yeast-derived product
% Dietary fiber (%β-glucan)	15.9 (6.8)	86 (85–90)
% Nonfiber carbohydrate	50	9
% Fat	7.0	0.0
% Protein	17.3	< 1.0
% Simple sugars	3.0	0.0
% Moisture	9	4
% Ash	3	< 1
Calories/g	3.97	3.6
β-glucan linkage	(1→3) (1→4)	(1→3) (1→6)
Solubility	High	Low
Viscosity	Moderate to high	Low
3 g of β-glucan is found in	44 g	3.5 g

Based on References 16 and 17.

β-glucan, patented under the name Fibercel® (Table 1). This purified β-glucan can be produced from baker's or brewer's yeast (*Saccharomyces cerevisiae*) in a process that is consistent with the Food and Drug Administration (FDA) requirements for food-grade products. The intracellular contents are hydrolyzed, preserving the β-glucan portion of the cell walls as discrete, intact, porous, hollow microspheres of 3 to 5 μm in diameter. The final product is 85% β-glucan by weight and consists of a β-(1→6)-branched-, β-(1→3)-linked linear glucose polysaccharide. Typically, branching occurs with β-(1→6) chains at a frequency of 5% for every 20 glucose molecules linked by β-(1→3) chains. The remaining 15% of the product is glycogen as α-(1→4) glucose, chitin as β-(1→4) *N*-acetyl glucosamin, and water. The product is 30% soluble fiber and 70% insoluble fiber, which gives it a creamy rather than gummy character.

Yeast-derived β-glucan is more palatable than the oat-bran-derived β-glucan, and unlike the latter β-glucan is tasteless, odorless, colorless, not water soluble, and therefore nongelling, even after heating and cooling. The product is heat stable (121°C for 30 min), pH stable (between 2 and 12), and shear stable, because most of the β-(1→3) linkages are insoluble, unlike the soluble β-(1→4) linkages found in oat-bran. This attribute is of particular importance because the yeast-derived product can readily mix with liquids without gelling or forming an unpalatable viscous mass. The yeast-derived product when added to liquids has a creamy mouthfeel. Table 2 lists the physical properties of the yeast-derived β-glucan.

The product meets the specifications for "yeast glucan" as defined in the FDA guidelines for approved food additives.[17] This permits its use in such products as salad dressings, frozen desserts, sour cream, cheese spreads, and the like. The licensees of the patent of the yeast fiber are planning to self-affirm a Generally Recognized as Safe (GRAS) status in 1998.[18]

III. MECHANISMS OF ACTION OF β-GLUCANS: LIPID-LOWERING EFFECT

A. Oats

Four mechanisms have been proposed to explain how β-glucan from oats lowers serum cholesterol. First, it has been postulated that soluble fiber binds to bile acids in the intestinal lumen, which results in a reduced bile acid pool

TABLE 2
Physical Properties of Yeast-Derived Fiber

> 95% whole particles
3–5 μm particle size
Nongelling
Heat stable (121°C for 30 min)
pH stable (2–12)
Highly miscible in aqueous and oil-based solutions
Moderately hydrophilic (8–10 ml water/g dry powder)
Forms creamy fat-like aqueous suspensions
Neutral taste
No odor
Low viscosity
High mechanical shear strength
Excellent "mouth-feel"

Based on Reference 17.

circulating back to the liver. This binding action stimulates production of more bile acids derived from cholesterol that is either made endogenously or captured from the circulation.[19-22] Only a small amount of cholesterol is excreted in the feces with the bile acids so that fecal losses do not contribute appreciably in lowering serum cholesterol concentrations.[20]

Second, soluble fibers are fermented in the large bowel by colonic bacteria.[19,22-24] This action results in the production of the short-chain fatty acids (SCFAs) — acetate, propionate, and butyrate. These SCFAs are absorbed through the portal vein, inhibiting hepatic cholesterol synthesis by limiting the action of HMG-CoA reductase (the rate-limiting enzyme required for cholesterol biosynthesis) or by increasing catabolism of LDL-C. However, in a recent letter on the subject, others caution that only one of three published studies in humans confirms the cholesterol-lowering effects of one of the SCFAs (propionate).[21]

Third, soluble fiber may delay gastric emptying, thereby reducing post-prandial serum insulin concentrations.[16] This action reduces hepatic cholesterol production through mediation of HMG-CoA reductase.

Fourth, oat soluble fiber may interfere with the absorption of dietary fat, including cholesterol, by increasing intestinal viscosity.[16] The increased viscosity causes the digesta to hold on to extra water, which slows its movement.

B. Yeast-Derived

Some of the proposed mechanisms by which oat β-glucan affects serum lipids are similar to those of the yeast-derived β-glucans. There appears to be some binding of the yeast-derived β-glucan to the bile acids in the small bowel. Similarly, SCFA production is increased, and serum insulin is reduced.

Yeast-derived β-glucans may also potentiate immune function.[17] Whole glucan particles have been identified in the lymphatic system of animals receiving this product, which might influence the function of so-called "scavenger" macrophages in atherosclerotic plaque development.

IV. HEALTH CLAIMS

In March of 1995, the Quaker Oats Co., Barrington, Ill., petitioned the United States Food and Drug Administration (FDA) for permission to make a health claim that oat products may reduce the risk of heart disease; the petition was granted in January 1997. This was the first time that such a claim was allowed for a specific food. The FDA reviewed over 37 studies demonstrating that oat-bran (and in particular β-glucan) lowered serum cholesterol. The claim is as follows: "Soluble fiber from oatmeal, as part of a low saturated fat, low cholesterol diet, may reduce the risk of heart disease."

The FDA determined that, on average, 3 g of β-glucan must be consumed per day to achieve a clinically relevant serum cholesterol-lowering effect (Table 3). The claim now relates only to oat products containing 0.75 g of β-glucan per serving. The effects of barley on risk for heart disease may be allowed in the future with additional clinical studies.

Yeast-derived β-glucan is required in portions with lesser calories to meet target amounts.

TABLE 3
Amount of Oats and Yeast to Yield 3 g β-Glucan

Food Item	Servings per day to meet 3 g β-glucan	kcal	Pounds gained per year (assuming 3500 kcal/pound) and not consumed as a replacement to a starch serving
Quaker Oat-Bran Hot Cereal	1 cup cooked	150	16
Old Fashioned Quaker Oats	1 1/2 cups cooked	225	23
Quick Quaker Oats	1 1/2 cups cooked	225	23
Quaker Oat-Bran Cold Cereal	A little more than 1/2 cups	150	16
Instant Quaker Oatmeal	3 packets	300	31
Yeast-derived fiber	3.5 g	< 10	1

Taken from product information, Quaker Oats Company, Barrington, Ill., 1997.

Because it can be added to a variety of foods (e.g., ice cream, cheese, spreads, soups, sauces, puddings, and salad dressings), consumers can take in the necessary amounts of lipid-lowering β-glucan in foods typically eaten in a normal day. Because the β-glucan can also function as a fat substitute, there is a potential for fewer total calories to be consumed.

V. TOLERANCE TO β-GLUCANS

A few subjects in clinical studies using oat products reported mild to moderate gastrointestinal symptoms, yet compliance was high with products from oats. None were reported in the single study using yeast-derived β-glucan.[25] Beer et al.[26] observed that one of the 14 subjects (7%) experienced gastrointestinal problems lasting 2 days during the 14-day study period. No dropouts or side effects were reported in a 19-subject study using purified β-glucan mixed in a liquid consumed twice daily for 2 weeks.[27] The subjects were advised, however, to consume the beverage immediately after mixing, because as viscosity increases palatability decreases, progressively up to a maximum of about 15 min.

The impact of even the possibility of gastrointestinal distress may compromise the "blindness" of the study design. Eighteen of the 20 subjects in another study[28] were able to guess which treatment they were randomly assigned to receive because they experienced gastrointestinal reactions, including flatulence, cramping, bloating, loose stools, and diarrhea. Subjects either consumed 87 g of oat-bran or a comparable fiber amount of wheat bran product daily for 6 weeks. No side effects were reported during the control phase when a low-fiber, refined wheat supplement diet was consumed.

One problem with oat products is that large amounts must be consumed to achieve statistically and clinically relevant reductions in serum cholesterol levels (Table 3); consumption of such a product containing 3 g of β-glucan at one time can be expected to produce gastrointestinal side effects in many individuals. In fact, the product literature from Quaker Oat Company suggests that their oat products be eaten several times throughout the day.

VI. OAT PRODUCTS: EFFECT ON SERUM LIPIDS

A. Hypercholesterolemic Subjects (Table 4)

1. 1963

The first report in free-living volunteers to test the effect of rolled oats on serum cholesterol

TABLE 4
Summary of Studies on Oat Products and Their Cholesterol-Lowering Effect

Initial serum cholesterol as mmol/l (mg/dl)	Free-living (FL) or metabolic ward (MW)	Number of patients	Oat product/ β-glucan[a]	Duration of study (weeks)	% total cholesterol decrease mmol/l (mg/dl) decreased	%LDL-C+ decrease mmol/l (mg/dl) decreased	Ref.
6.49 (251)	FL	21	140 g rolled oats/5.9 g	3	11/0.72 (28)	N/A	29
6.69 (269)	MW	8	100 g oat-bran/6.8 g	10 days	13/0.91 (35)	14/0.65 (25)	22
7.24 (280)	MW	20	100 g oat-bran/6.8	3	19/1.04 (54)	23/1.06 (41)	23
6.21 (240) oat-bran and 7.09 (274) POB[b]	FL	68	50 g oat-bran/3.4 g and 42.5 POB/3.4	12	13/0.93 (36) oat-bran and 10/0.72 (28)	N/A	30
Range from 4.91 (190) to 8.97 (347)	MW	20	110 g oat-bran/7.5 g	3	12.8/ N/A	12.1/ N/A	31
6.18 (239)	FL	119	56 g oat-bran/3.8 g	6	6/0.30 (15)	9/0.36 (14)	24
N/A	Meta-analysis based on 20 trials	16 to 137 subjects per study	Variable	18 days to 12 weeks	2 to 3/0.13 (5) to 0.16 (6)	N/A	14
6.78 (262)	FL	19	70 g purified oat-bran/5.8 g	4	9/0.62 (24)	10/0.47 (18)	27

Note: 100 g oatmeal (dry) contains 4.2 g β-glucan, 5.1 g soluble fiber, and 5.2 g insoluble fiber; 100 g oat-bran (dry) contains 6.8 g β-glucan, 6.3 g soluble fiber, and 9.6 g insoluble fiber.

[a] Low-density lipoprotein-cholesterol.
[b] Processed oat-bran.

Based on Reference 16.

levels was published in 1963.[29] The study included 21 male subjects aged 30 to 50 years and took place over a 3-week period. The subjects consumed 300 g of an experimental bread containing 140 grams of rolled oats instead of the normal bread of their daily diets. Total cholesterol concentrations were determined weekly, starting 3 weeks before the experiment and ending 3 weeks afterward. The serum cholesterol levels of the volunteers decreased by 5%, from 6.49 mmol/l (251mg/dl) to 6.18 mmol/l (239 mg/dl), after only 7 days of the oat diet. The trend continued downward to 5.77 mmol/l (223 mg/dl) at the end of 3 weeks for a total reduction of 11%. When the bread containing rolled oats was replaced with normal wheat-based bread, serum cholesterol immediately rose and reached 6.36 mmol/l (246 mg/dl) after 2 weeks.

Interestingly, the authors thought that the relatively high fat content (35%) of the particular oats used in this contributed to the hypocholesterolemic effect. (Oats are typically 15% fat.) Experiments were conducted in animals subsequently, using rolled oats with their natural fat, and defatted rolled oats with added corn oil or coconut oil. As postulated, oats with corn oil lowered cholesterol to the same extent as rolled oats with their natural fat did; oats with added coconut oil raised serum cholesterol levels.

2. 1981–1984

A couple of decades later researchers evaluated selected metabolic effects in previously documented hypercholesterolemic men after consumption of plant fibers (oat-bran vs. control diets).[22] Eight men, whose serum cholesterol concentration had exceeded 6.72 mmol/l (260 mg/dl) on two previous occasions, were studied. The two eucaloric diets differed only in the inclusion of 100 g of oat-bran in the test diet, which was provided in muffins and hot cereals for 10 days. Serum concentrations of total cholesterol, triglycerides, and blood glucose levels were measured daily after a 10-h fast. At the end of each dietary regimen, HDL-C and calculated levels of LDL-C were measured.

The total serum cholesterol concentrations decreased significantly (13%; $p < 0.01$) (6.96 ± 0.41 mmol/l [269 ± 16 mg/dl] to 6.05 ± 0.49 mmol/l [234 ± 19 mg/dl]) with oat-bran diets but remained unchanged with control diets. The LDL-C concentrations with the oat-bran diets decreased from the initial mean of 4.75 ± 0.36 mmol/l (184 ± 14 mg/dl) to 4.11 ± 0.44 mmol/l (159 ± 17 mg/dl). With the control diet, there were no changes in blood lipids. HDL-C concentrations were not altered in either group. Decreases in cholesterol concentrations were greater than in the previous study,[29] perhaps because the diets were better controlled in a metabolic ward, and more β-glucan was provided. Moreover, mean initial serum cholesterol concentrations were larger, which may have contributed to the larger percentage decline.

Later, 20 hypercholesterolemic men (serum levels of total cholesterol greater than 6.72 mmol/l [260 mg/dl]) aged 34 to 66 years were studied in a metabolic ward.[23] Seven patients were considered to be overweight (> 20% over desired body weight). None had received hypolipidemic agents in the 3 months preceding the study. Subjects were randomly assigned to receive identical diets except for plant fiber that came from oats or beans. Participants received a control diet for 7 days and then a test diet for 21 days. All diets contained 20% of energy as protein, 43% as carbohydrate, and 37% as fat with approximately 430 mg of cholesterol per day. The control diet contained 19 g plant fiber and 6 g soluble fiber per day. The oat-bran diet included 100 g of oat bran per day served as a bowl of hot cereal (36 g oat-bran) and five oat-bran muffins per day (62 g oat-bran). This supplied approximately 47 g total plant fiber and 17 g soluble fiber. The bean diet contained 115 g of dried beans (pinto and navy) per day, which provided approximately the same amount of total fiber and soluble fiber as did the oat-bran diet.

Patients lost approximately 0.4 kg/week during the oat-bran diet, but not during the

bean-supplementation phase, despite identical energy intakes. During the oat-bran diet, total cholesterol decreased from 7.24 ± 0.41 mmol/l (280 ± 16 mg/dl) to 5.84 ± 0.28 mmol/l (226 ± 11 mg/dl) (19%; $p < 0.0005$), and LDL-C decreased from 4.91 ± 0.31 mmol/l (190 ± 12 mg/dl) to 3.85 ± 0.23 mmol/l (149 ± 9 mg/dl) (23%; $p < 0.0025$). With the bean diet, total cholesterol decreased from 7.76 ± 0.34 mmol/l (300 ± 13 mg/dl) to 6.30 ± 0.34 mmol/l (244 ± 13 mg/dl) (19%; $p < 0.0005$), and LDL-C decreased from 5.72 ± 0.36 mmol/l (221 ± 14 mg/dl) to 4.40 ± 0.31 mmol/l (170 ± 12 mg/dl) (24%; $p < 0.0005$). The authors concluded that oat-bran- and bean-supplemented diets may play an important role in the nutritional management of some hypercholesterolemic patients.

This study and the previous one[22] used 0.9 g more β-glucan and achieved greater reductions in serum cholesterol concentrations than DeGroot et al.,[29] who did not house subjects in a metabolic ward. The initial serum cholesterol concentrations were higher in this study than in DeGroot et al.,[29] which may also have contributed to the large decrease in serum lipids from oats.

3. 1990–1992

The next major study in hypercholesterolemic subjects assessed the effect of a low-fat, low-cholesterol diet and oat products on serum lipids.[30] The subjects — 68 free-living men and women between the ages of 20 and 65 years — had mean serum cholesterol concentrations greater than 7.00 ± 0.13 mmol/l (271 ± 5 mg/dl). The subjects were randomly assigned to one of four groups: low-fat, low-cholesterol diet (LFLC); low-fat, low-cholesterol diet plus 50 g/day oat-bran (LFLC + OB); 50 g/day oat-bran-supplemented regular diet (OB); or 42.5 g/day of processed oat bran (POB) (ready-to-eat cereal) plus a regular diet. The β-glucan in OB and POB were equal, about 3.4 g. At 4-week intervals, total serum cholesterol and HDL-C levels were measured and diet analyses performed.

All subjects experienced significant reductions ($p < 0.05$) in serum cholesterol concentrations. Reductions were as follows: 7.00 ± 0.13 mmol/l (271 ± 5 mg/dl) to 5.82 ± 0.21 mmol/l (225 ± 8 mg/dl) for LFLC (17%); 7.18 ± 0.21 mmol/l (278 ± 8 mg/dl) to 6.10 ± 0.26 mmol/l (236 ± 10 mg/dl) for LFLC + OB (13%); 7.37 ± 0.20 mmol/l (285 ± 8 mg/dl) to 6.44 ± 0.21 mmol/l (249 ± 8 mg/dl) for OB (12%); and 7.11 ± 0.18 mmol/l (275 ± 7) to 6.36 ± 0.23 mmol/l (246 ± 9 mg/dl) for POB (10%). Each reduction was evident within the first four weeks of treatment, and serum cholesterol levels stabilized between weeks 4 and 12. In these individuals, serum lipids decreased comparably to those in another study of free-living subjects[29] and those in a study where subjects were housed in a metabolic ward,[22] although the β-glucan used was half that of one study[22] and 58% of the other.[29] The initial mean serum cholesterol levels were greater in the present study, again perhaps accounting for the similar decrease despite using less β-glucan.

In the next study, 20 hypercholesterolemic men (fasting serum cholesterol concentrations from 4.91 mmol/l (190 mg/dl) to 8.97 mmol/l (347 mg/dl) were admitted to a metabolic ward and randomly assigned to a diet with either 110 g OB or 40 g wheat bran (WB) for 21 days after a 7-day control-diet period.[31] The mean age was 57 ± 10 years for the oat-bran group and 65 ± 5 years for the wheat-bran group. The dietary regimens were designed to be identical in energy content and nutrients, differing only in the amount of soluble fiber. Oat-bran contained 34 g total dietary fiber (TDF) of which 13.4 g was soluble. The WB contained 34 g of TDF of which 7.8 g was soluble.

After 21 days, subjects taking OB showed a significant decrease ($p < 0.001$) in total cholesterol levels (12.8 ± 2.2%). The LDL-C decreased 12.1 ± 3.5% ($p < 0.005$). Those consuming WB had no change in these blood lipids. HDL-C levels did not change significantly in either group. These decreases in total cholesterol and LDL-C were comparable to those of other subjects — both free-living[29,30]

and in metabolic wards[22] — in other studies. The amount of β-glucan used in this study exceeded that in the comparable studies reviewed so far. Because initial mean total serum cholesterol levels were not reported, no comparison of these values is possible.

In the same year, the results of a large study, including 119 male and female subjects aged 20 to 70 years with similar mean baseline total cholesterol levels, were reported.[24] The study was randomized, controlled, blinded, with a crossover design using oat-bran (28 g [1 oz.]) twice daily vs. wheat cereal for 6 weeks. There was also an initial 6-week stabilization period. Subjects followed the NCEP Step 1 diet, and eating behavior was monitored throughout the study period. Blood lipid decreased most in the oat-bran group, followed by wheat (3% decrease in total cholesterol) and by diet alone (1% decrease in total cholesterol). Total cholesterol in the OB group went from 6.18 ± 0.65 mmol/l (239 ± 25 mg/dl) to 5.79 ± 0.70 mmol/l (224 ± 27 mg/dl) (6%), and LDL-C from 4.19 ± 0.65 mmol/l (162 ± 25) to 3.83 ± 0.70 mmol/l (148 ± 27 mg/dl) (9%).

This study was the first to demonstrate a significant age and gender difference ($p = 0.001$). Women under 50 showed virtually no response to the oat-bran, while older women showed a marked drop in LDL-C levels (–0.36 ± 0.44 mmol/l [–14.3 ± 17.0 mg/dl]). Younger men (under age 50) had an intermediate response to OB (–0.23 ± 0.41 mmol/l [–9.3 ± 15.5 mg/dl]), while men of 50 or older had only a –0.08 ± 0.36 mmol/l (–3.1 ± 14.3 mg/dl decline). Others[14] who conducted a meta-analysis did not find the same effect, perhaps because there were only a few subjects in many of the groups (i.e., low statistical power). The declines in serum cholesterol in Keegan et al.[24] were roughly one-half of what has been reported elsewhere.[22,23,29,30] Because the subjects in this study[24] were free-living, compliance with the dietary regimens may have waned. However, others[29,30] have reported better lipid-lowering effects in free-living subjects. Demark-Wahnefried et al.[30] used about the same amount of β-glucan, and the other group[29] used 1.6 times more. The most likely explanation for the small changes in serum lipids from oats was that the starting mean serum cholesterol concentrations were lower than in the other studies reviewed.[22,23,29,30]

The most conclusive study on the effect of oats on serum lipids was a meta-analysis.[14] The investigators formally summarized the oat-product literature on clinical trials of free-living subjects as of March 1991, noting whether blood cholesterol response varied by dose or initial blood cholesterol level or both. Trials were included only if they were randomized and controlled, assessed dietary behavior and body weight changes, contained the raw data, and published sufficient information to perform the necessary calculations. Twenty trials were identified, but most analyses were based on 12 trials, which accounted for 22 effect sizes (mean change in total cholesterol concentrations).

Subjects ranged in age from 20 to 73 years. The duration of treatment ranged from 18 days to 12 weeks, and 10 to 137 subjects were enrolled in the treatment and control groups. Most of the trials assessed the diet by means of a 3- or 4-day written food record.

In these 12 trials, total cholesterol levels declined –0.13 mmol/l (–5.1 mg/dl) (SE, 0.03 mmol/l [1.12 mg/dl], with a 95% confidence interval [CI] of –0.19 to –0.017 mmol/l [–7.3 to –2.9 mg/dl]). The summary effect size for trials using wheat control groups was –0.11 mmol/l (–4.4 mg/dl) (95% CI, –0.21 to –0.01 mmol/l [–8.3 to –0.38 mg/dl]). Fivefold reductions in total cholesterol levels were observed in the trials of subjects with higher baseline blood cholesterol levels (≥ 5.92 mmol/l [≥ 229 mg/dl]) or when subjects consumed 3 g or more of soluble fiber from oats. This contrasted with other studies where subjects had lower baseline serum cholesterol levels and consumed lower amounts of fiber. The reduction in effect size per unit of baseline total cholesterol level was –0.14 (SE, 0.037, $p = 0.001$). Age, gender, and the interaction between the two failed to predict the response of serum

cholesterol concentrations to oat consumption. This report provided the strongest evidence to the FDA that about 3 g per day of soluble fiber from oat products can lower the total cholesterol level by 5 to 6 mg/dl, and that the reduction is greater in those with higher initial blood cholesterol levels. Thus, a patient with a serum cholesterol level of 6.47 mmol/l (250 mg/dl) who takes 3 g of soluble fiber from oats for at least 18 days can expect this level to decrease to 6.34 mmol/l (245 mg/dl) (2%). Apparently, small reductions in serum cholesterol concentrations such as these result in lowered heart disease mortality.[8,9]

4. 1994–Present

Braaten et al.[27] were the first to appreciate the importance of β-glucan extracted from oats as the active agent for modulating blood lipids. In a randomized crossover design study, 20 free-living hypercholesterolemic males and females were randomly assigned to two groups. One consumed the experimental powder dispersed in a beverage (2.9 g β-glucan) and the other a beverage containing a maltodextrin placebo twice daily for 4 weeks after a 3-week washout period. The product was 80% β-glucan derived from oat gum. The gum was used in an attempt to standardize the amount of β-glucan administered; oats contain variable amounts of β-glucan. Nineteen subjects completed the study. Baseline mean total and LDL-C levels phase were 6.77 ± 0.16 mmol/l (262 ± 6 mg/dl) and 4.62 ± 0.16 mmol/l (179 ± 6 mg/dl), respectively, which decreased significantly to 6.15 ± 0.16 mmol/l (238 ± 6 mg/dl) ($p < 0.001$; 9%) and 4.16 ± 0.15 mmol/l (161 ± 6 mg/dl) ($p < 0.001$; 10%), respectively, at week 4.

When the β-glucan was discontinued, total and LDL-C returned to initial levels. In this study, use of 5.8 g of β-glucan yielded a decrease in total cholesterol similar to that of DeGroot,[29] who used similar amounts. Others[22,23,30] used more β-glucan and found higher reductions in total serum cholesterol concentrations. In contrast to those in previous reports,[22,23,31] the reductions in this study in total and LDL-C levels occurred in the absence of any dietary restrictions. Dietary supplementation with purified β-glucan may be an effective way to reduce dietary lipids in hypercholesterolemic patients, who typically follow a heart-healthy diet.

B. Normocholesterolemic Subjects

Oats to be appear effective in lowering cholesterol in hypercholesterolemic subjects, but normocholesterolemic subjects do not always experience the same effect. This is important because products containing β-glucan are widespread in the food supply. Unfortunately, studies evaluating normocholesterolemic subjects typically do not show lipid-lowering effect of oat products. This may lead to confusion on the part of the public.

Investigators evaluated the effect of oat-bran in persons with normal serum cholesterol levels.[28] Diets were supplemented with isocaloric amounts of a high-fiber oat-bran (87 g per day) and of a low-fiber refined-wheat product. Twenty healthy subjects, 23 to 49 years old, all of whom had initial total serum cholesterol levels of 4.73 ± 0.80 mmol/l (186 ± 31 mg/dl) and LDL-C of 2.97 ± 0.59 mmol/l (115 ± 23 mg/dl), were included in the study. Following a 1-week period in which subjects consumed their customary diets, the subjects consumed one supplement for 6 weeks, then the other for the same time, in a double-blind crossover design. Serum cholesterol and LDL-C decreased significantly following each dietary intervention. In the oat-bran group, total cholesterol decreased to 4.45 ± 0.72 mmol/l (172 ± 28 mg/dl) (–7%; $p < 0.05$) and LDL-C to 2.69 ± 0.62 mmol/l (104 ± 24 mg/dl) (–10%; $p < 0.05$). Similarly, in the low-fiber wheat-product group, cholesterol levels decreased to 4.45 ± 0.65 mmol/l (172 ± 25 mg/dL) (–8%; $p < 0.05$) and LDL-C to 2.77 ± 0.59 mmol/l (107 ± 23 mg/dl) (–7%; $p < 0.05$).

The authors attribute these findings to the fact that the subjects ate less saturated fat and

more polyunsaturated fats during both periods of dietary intervention. It appeared that these changes were sufficient to explain the significant reduction in blood lipid levels. Both dietary treatments were high in complex carbohydrates, which seemed to replace foods that could have raised blood cholesterol levels. It was concluded from this study that oat-bran may have no cholesterol-lowering effects, especially on normocholesterolemic subjects.

In contrast to these results,[28] the addition of 100 g of oat-bran to diets of subjects with normal serum lipids resulted in significant reductions.[32] The study included 9 men (23.8 ± 2.2 years old) who consumed a constant low-fiber diet for 1 month. During the second month, they consumed the same diet with the addition of 100 g/day of oat-bran as hot or cold cereal (Quaker Oats Company, Barrington, Ill.). Dietary fiber intake with oat-bran was 33.9 ± 1.5 g/day, of which 10.3 ± 0.4 g/day was soluble fiber. (The oat-bran used had 16.1% total dietary fiber of which 38% was [1→3] [1→4] β-glucan and 46% soluble fiber.)

Bile acid kinetics was determined by measurement of ^{13}C enrichment of serum cholic acid (CA) and of chenodeoxycholic acid (DCA). Blood samples for total serum cholesterol and triglyceride analyses were drawn 1 day before study (baseline) and on days 7, and on days 27 and 28, and days 55 and 56, for the low- and high-fiber measurements, respectively.

Serum cholesterol levels decreased in all subjects. In the low-fiber group, the mean serum cholesterol concentration went from 4.58 ± 1.03 mmol/l (177 ± 40 mg/dl) to 3.93 ± 0.72 mmol/l (152 ± 28 mg/dl) (14%; $p < 0.01$). During the high-fiber supplementation, the mean serum cholesterol level went from 3.93 ± 0.72 mmol/l (152 ± 28 mg/dl) to 3.57 ± 0.78 mmol/l (138 ± 30 mg/dl) (9%; $p < 0.01$).

Incorporation of oat-bran into the constant diet substantially altered the kinetics of both primary bile acids. The synthesis and the fractional turnover rates of CA and DCA increased significantly ($p < 0.05$). The pool size of DCA more than doubled ($p < 0.01$) and the pool size of CA decreased ($p < 0.05$). Total daily bile acids in the feces more than doubled ($p < 0.05$). This was the first report to demonstrate that increased bile acid synthesis and decreased bile acid absorption are two mechanisms by which oat bran lowers serum cholesterol levels in healthy individuals. The substantial increase (79%) observed in the proportion of the total bile acid pool that was DCA was consistent with the hypothesis that there was an alteration not only in hepatic bile acid synthesis but also in cholesterol synthesis and absorption.

Later, others evaluated the effect of oat-gum on serum lipids.[26] Fourteen healthy young men were randomly assigned to receive daily either the equivalent of 150 g of oat-bran (in the form of oat-gum providing 9 g of β-glucan) or a placebo. Both were served in a flavored instant whip. Exclusion criteria were hypertension, hyperlipidemia, use of medication that affect blood pressure or serum lipid levels, obesity, excessive alcohol use, and smoking. Initial serum cholesterol values ranged from 3.89 mmol/l to 5.43 mmol/l (150 to 210 mg/dl). Intervention lasted 14 days, followed by an equal crossover period. All meals were prepared in a metabolic kitchen. Total cholesterol and LDL-C concentrations did not change during the oat gum phase; HDL-C rose significantly ($p < 0.05$).

The oat-gum preparation used in this study contained a highly concentrated source of β-glucan (62%). At first blush, it appeared that even large quantities of β-glucan (9 g per day) from a uniform source do not reduce serum lipids levels. However, the authors argue that the total amount of β-glucan is not as important as its solubility and molecular weight. Highly soluble β-glucans, with moderate to high molecular weights (> 100 kDa), appeared to reduce serum cholesterol levels better than those of low solubility and low molecular weight. Beta-glucans with higher solubility and molecular weight create more viscosity in the intestinal lumen, which is the required environment to induce serum cholesterol lowering. Increased viscosity in the gut leads to a so-called unstirred layer adjacent to the

mucosa. This layer may serve as a physical barrier to nutrient absorption and bile acid reabsorption. However, viscosity is important only when the soluble form of β-glucan is ingested. Yeast-derived β-glucan is low in viscosity and mostly insoluble, but still lowers serum cholesterol levels, perhaps due to its still substantial (30%) amount of soluble fiber.

C. Summary of Studies on Oats and Their Lipid-Lowering Effect

Of the studies summarized in Table 4, oats lower serum cholesterol concentrations by between 2 and 19%. Not summarized was one small study (n = 12) of hypercholesterolemic subjects showing an identical effect on lipid for oat-bran and wheat-bran.[33] These authors ascribed the decline in serum lipids to dietary fiber. Diets were controlled so that fat was not displaced with the fiber sources. However, this study used a New Zealand oat product that may differ from products in the U.S.

The variability of the studies can be attributed to differences in oat β-glucan content, oat fiber solubility, and initial serum cholesterol concentration. The more β-glucan, the higher the solubility; and the higher initial blood cholesterol levels would likely produce more significant results. It was not until the early 1990s that there was a standard of identity for oat products; thus, subsequent studies should be more uniform.[15]

VII. YEAST-DERIVED β-GLUCANS: EFFECT ON SERUM LIPIDS

To date, there have been several animal studies[17] and one clinical[25] and another using the yeast-derived β-glucan. Only the clinical data are presented here.

A. Clinical Trial

Fifteen obese hypercholesterolemic males (serum cholesterol greater than 6.21 mmol/l [240 mg/dl]) were included in the study.[25] After a 3-week period in which subjects ate their usual diet, 15 g per day of yeast fiber was added to the diet for 8 weeks and then stopped for 4 weeks. Weekly 3-day food records were kept, and plasma total cholesterol and lipoprotein cholesterol concentrations were measured weekly during baseline, and at week 6, 7, and 8 of fiber consumption, and 4 weeks after cessation of the fiber. Patients maintained the same body mass indices during the study. Compared with baseline, yeast fiber consumption significantly reduced plasma total cholesterol at week 7 (8%, $p < 0.05$) and at week 8 (6%, $p < 0.05$) using Bonferroni correction. The total cholesterol concentration at baseline did not differ from week 12 levels. No significant differences were noted between baseline LDL-C and weeks 7, 8, or 12 when comparing individual groups using Bonferroni correction even though the overall one-way ANOVA with repeated measures was highly significant ($p < 0.0001$). The level of LDL-C did decline 8% at week 8 when compared with baseline. There was a significant effect of diet on HDL-C ($p < 0.005$ by one-way ANOVA with repeated measures). However, a group difference was only observed between baseline and week 12 (16% increase, $p < 0.05$ by Bonferroni correction). The triglycerides did not change. No adverse gastrointestinal effects were observed. The results of this study demonstrated that the yeast derived β-glucan significantly lowered total cholesterol levels while being well tolerated; the HDL-C concentration rose as well, but only 4 weeks after the fiber had stopped. This provided a more favorable TC/HDL-C ratio. This product appears to be safe and may have a role as a dietary supplement, with salutary health effects for improving serum lipid profiles.

CONCLUSION

There are sufficient data to support the use of oat products to lower serum cholesterol levels and to reduce the risk of heart disease.

Yeast-derived β-glucan appears to have the same effect on blood lipids and has the advantage of being more concentrated so that fewer calories need to be ingested. The yeast-derived β-glucan is considerably more versatile than oat products because it can be readily incorporated into a variety of foodstuffs. Obviously, more clinical research is needed to confirm the extent of cholesterol-lowering effects of this source of β-glucan. At present, yeast β-glucan and oats can lower TC and LDL-C and thus reduce the risk of developing heart disease.

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4th European Symposium on Oats—Oats and Healthy Foods

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The food uses of oats has been the topic of European conferences held in Helsinki, Finland (1998), Cambridge, England (1999), and Uppsala, Sweden (2001). The 4th European Symposium on Oats—Oats and Healthy Foods was held in Brussels, Belgium, February 15–16, 2006. More than 50 professionals from industry and academia attended the two-day symposium organized by Cereals&Europe and endorsed by AACC International to discuss current issues relating to oat soluble fiber, health claims, analytical issues, and the suitability of oats for celiac patients. Novel food applications for oats were presented by invited speakers and during a tasting session.

Oats have a well-known, positive image in Northern and Central Europe. Recent clinical data seem to bolster the position that oats are a "naturally functional food ingredient" with cholesterol-lowering and glycemic response-attenuating properties, as well as other properties associated with whole grains.

In his informative overview of health claims and the European regulatory situation, David Richardson (DPR Nutrition Ltd., U.K.) introduced "substantiation based on generally accepted scientific data" and "well understood by the average consumer" as concepts being used in the preparation of new European legislation. Given the claims that already exist (i.e., the U.S. FDA claim that oats "may reduce risk of heart disease" [1997]; the U.K. JHCI claim that oats "can help to reduce cholesterol" [2004]; and the two Swedish SNF claims that oat "may help reduce cholesterol" and "reduces blood glucose and insulin response" [2001 and 2002, respectively]), a European health claim for oats seems warranted. John J. Smith (Quaker Oats, USA) emphasized that within the current whole-grain promotion and health claims for whole grains, oats have an exceptionally beneficial position with their β-glucan content.

Heli Anttila (University of Helsinki, Finland) presented the background and techniques for a novel viscometric procedure, based on the enzymatic hydrolysis of starch and protein and the measurement of the viscosity of the soluble fiber extract at increasing concentrations plotted against β-glucan content, that could complement the current analytical procedure for soluble dietary fiber. Adrian Meyer (CreaNutrition, Switzerland) showed how clinical data and health claims have increased the demand for oat bran products that are high in β-glucan. In 2005 the Dutch Voedingscentrum acknowledged that a multigrain bread containing β-glucan significantly reduces cholesterol.

Rickard Öste (CEBA AB, Sweden) explained the development of a dairy-free milk, containing only pure oats, water, and rapeseed oil, that is a leader in the Swedish nondairy products market. An oat-based yogurt-type product was described by Hannu Salovaara (University of Helsinki, Finland): cooked oat bran is fermented with probiotic bacteria, providing a dual benefit. The product leads the nondairy yogurt sector in Finland. Susan Lawlor (Glanbia Nutritionals, Ireland) introduced a soluble fiber concentrate, containing 54% oat β-glucan. This product was reported to increase intestinal viscosity, surpassing the effects of conventional oat products, as well as significantly reduce LDL cholesterol levels.

Although direct clinical evidence for the toxicity of its proteins has never been shown, there is some controversy concerning the use of oats in the diets of celiac patients. Several clinical studies have shown that regular oat flakes are well tolerated by individuals sensitive to gluten proteins, as discussed by Paul Ciclitira (Rayne Institute, U.K.). Possible contamination of oats with wheat, rye, or barley, the lack of analytical purity tests, and the possible presence

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of a sensitive subgroup among celiac patients all are reasons for concern. Peter Shewry (Rothamsted Research, UK) pointed out that the repetitive amino acid sequences of avenins resemble those of S-rich gliadins, but they do not contain any of the precise epitopes known to be active in celiac disease. This difference could be a potential explanation for why oats are suitable for celiac patients.

Päivi Kanerva (University of Helsinki, Finland) discussed the two commercially available immunological techniques (ELISA assays) to test for purity. The 1989 test, based on Ω-gliadin antibody, cannot detect barley and rye prolamins to the same extent as wheat gliadins. The 2003 method is based on a monoclonal antibody R5 raised against rye secalin and has an embedded risk of false-positive results and overestimation of contaminating prolamins present. Carola Lindholm (Lantmännen AS-Faktor AB, Sweden) described the strict control and production of pure oat flakes, as practiced by Cerealia/ Semper since 1999, that results in a maximum contamination of 20 ppm gluten (prolamin from wheat, rye, or barley).

The symposium showed that the potential present in oats has not been fully explored and utilized. The combination of scientific and commercial information presented during this symposium was inspiring and worth repeating.