Appendix 8

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Appendix 8
Comment C-1412

August 6, 1996

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Docket No. 95P-0197
Food Labeling: Health Claims; Oats and Coronary Heart Disease

Dear Sir or Madam:

I am writing to comment on a section of the Quaker Oats Company's supplemental comments to the above-reference docket which is entitled "Dividing the effective levels of the substance across three eating occasions...", which begins on page 4 of the supplemental comments. In this section, Quaker Oats contends that in order for the hypocholesterolemic effect of oat products to manifest it is necessary that an adequate amount of oats be present at each eating occasion. They cite a study done by us (Gallaher et al., J. Nutr. 123: 244-252, 1993) to support this contention. They state, in regard to our study, that when a high viscosity guar gum was compared to a low viscosity guar gum, there were significant differences in blood cholesterol and bile acid elimination, and that the low viscosity guar was not effective in lowering blood lipids. I have several comments regarding these statements, as follows:

1. While it is true that the guar gum-containing diet did lower plasma and liver cholesterol, it clearly did so only at the 6 week time period. There were no statistically significant differences in plasma cholesterol between the low and high viscosity guar gum diets at the 3 week and 11 week time periods and no significant difference in total liver cholesterol at the 11 week time period (we did not measure liver cholesterol at the 3 week period).

2. In a subsequent study published the same year as the one cited above (Gallaher et al., J. Nutr. 123: 1732-1738, 1993), we examined the effect of viscosity on plasma cholesterol in hamsters over a greater number of viscosities. This study, unlike the previous one, included a "no viscosity" control, i.e. a group fed cellulose was included. Several points became clear as a result of that work, as follows:

   a. Even very low intestinal viscosities can result in rather substantial decreases in plasma cholesterol. Plasma cholesterol dropped from 339 mg/dL in the cellulose group (viscosity of 2 cP) to 254 mg/dL in the low viscosity hydroxypropyl methylcellulose (HPMC) group (intestinal viscosity of 47 cP). Thus, the low viscosity guar gum group (LV-GG) in the first study (Gallaher et al., J. Nutr. 123: 244-252, 1993), which had an intestinal viscosity of 56 cP,

may well have had a lower plasma cholesterol relative to a cellulose group, had we included one in the study.

b. Thus, from a theoretical point of view, the shape of the curve of plasma cholesterol versus intestinal contents viscosity (Figure 2) indicates that, at low viscosities, any increase in intestinal contents viscosity will lower plasma cholesterol.

c. It is also true that in our first study (Gallaher et al., J. Nutr. 123: 244-252, 1993) we did report that bile acid excretion was less in the low viscosity guar gum group (LV-GG) compared to the high viscosity guar gum group (HV-GG). However, this difference did not quite achieve statistical significance. More importantly, though, we have since gone back and analyzed the bile acid and neutral sterol excretion in the animals from our second study (Gallaher et al., J. Nutr. 123: 1732-1738, 1993). The relationship between bile acid and neutral sterol excretion versus HPMC viscosity is shown in Figure 1. What becomes apparent is that it is not that high viscosities of HPMC increase bile acid excretion, but that at a low, but non-zero viscosity, there is less excretion of bile acids. This is an interesting and unexpected finding that suggests that at a low viscosity, bile acid reabsorption is enhanced, but as viscosity continues to increase this enhancement is lost.

d. What also becomes apparent is that as intestinal viscosity increases, neutral sterols also increases. The shape of the curve (Figure 1 attached) is essentially the inverse of the plasma cholesterol curve, which suggests that interference with cholesterol absorption is the primary mechanism by which increased viscosity lowers cholesterol. We have obtained essentially identical results in a recently published study (Carr et al., J. Nutr. 126: 1463-1469, 1996).

Although any increase in intestinal viscosity appears to effect a reduction in plasma cholesterol, clearly there must be a certain minim consumption of a viscosity-inducing food, such as oat cereal, to produce a biologically meaningful reduction in plasma cholesterol. What in my opinion remains unclear is whether dividing up this minimum amount of food across several meals will have a different impact on cholesterol lowering compared to consuming it as a bolus at one meal. That is, will inducing a larger decrease with cholesterol absorption at one meal produce greater plasma cholesterol lowering than inducing a smaller decrease in cholesterol absorption several times during the day. I do not believe our knowledge is sufficient to make this judgment.

Recently, we have examined the viscosity of intestinal contents supernatants produced by consuming several oat-based breakfast cereals. Rats were adapted to the AIN-76 diet for several days, fasted overnight, then given a meal. Two to three hours after the meal the rats were killed, the intestinal contents collected, centrifuged, and the viscosity of the supernatants measured at several shear rates. The protocol is essentially the same as the one described in our report of the effect of different viscosities of hydroxypropyl methylcellulose on plasma cholesterol concentrations in hamsters (Gallaher et al., J. Nutr. 123: 1732-1738, 1993). Viscosities values are either calculated at or extrapolated to a shear rate of 23 s^{-1}. As can be seen in Figure 2, consumption of General Mills Cheerios, Quaker One Minute Oatmeal (cooked or uncooked), and Quaker Oat Bran all resulted in a

relatively high intestinal contents viscosity. Whole oat flour had a far lower viscosity, suggesting that the processing involved in converting the whole oat flour into Cheerios (the main ingredient) alters the fiber material in such a way as to greatly increase it's viscosity. The level of viscosity achieved by all these cereals, if extrapolated to our hamster study cited above, would have produced a maximal reduction in plasma cholesterol. Since Cheerios, oatmeal, and oat bran have all been demonstrated to reduce plasma cholesterol in humans, I believe our viscosity results obtained in rats are applicable to the human situation. That is, I suggest that our results indicate that consumption of any of these cereals by humans, at their recommended serving size, would produce an intestinal viscosity sufficient to reduce cholesterol absorption and thereby lower plasma cholesterol. Further, I believe viscosity values obtained in animals may be useful as a predictor of the cholesterol-lowering potential of other foods containing certain soluble fibers.

I offer these comments in hopes they will be of assistance to FDA in finalizing the proposed rule to authorize the health claim related to oat products and lowered cholesterol/reduced coronary heart disease. I am also enclosing reprints of our studies on viscosity and cholesterol lowering in the anticipation that these would be useful to you. I would be happy to discuss these comments with you further.

Sincerely,

Daniel D. Gallaher

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Figure 1

Effect of Intestinal Contents Viscosity On Bile Acid and Neutral Sterol Excretion

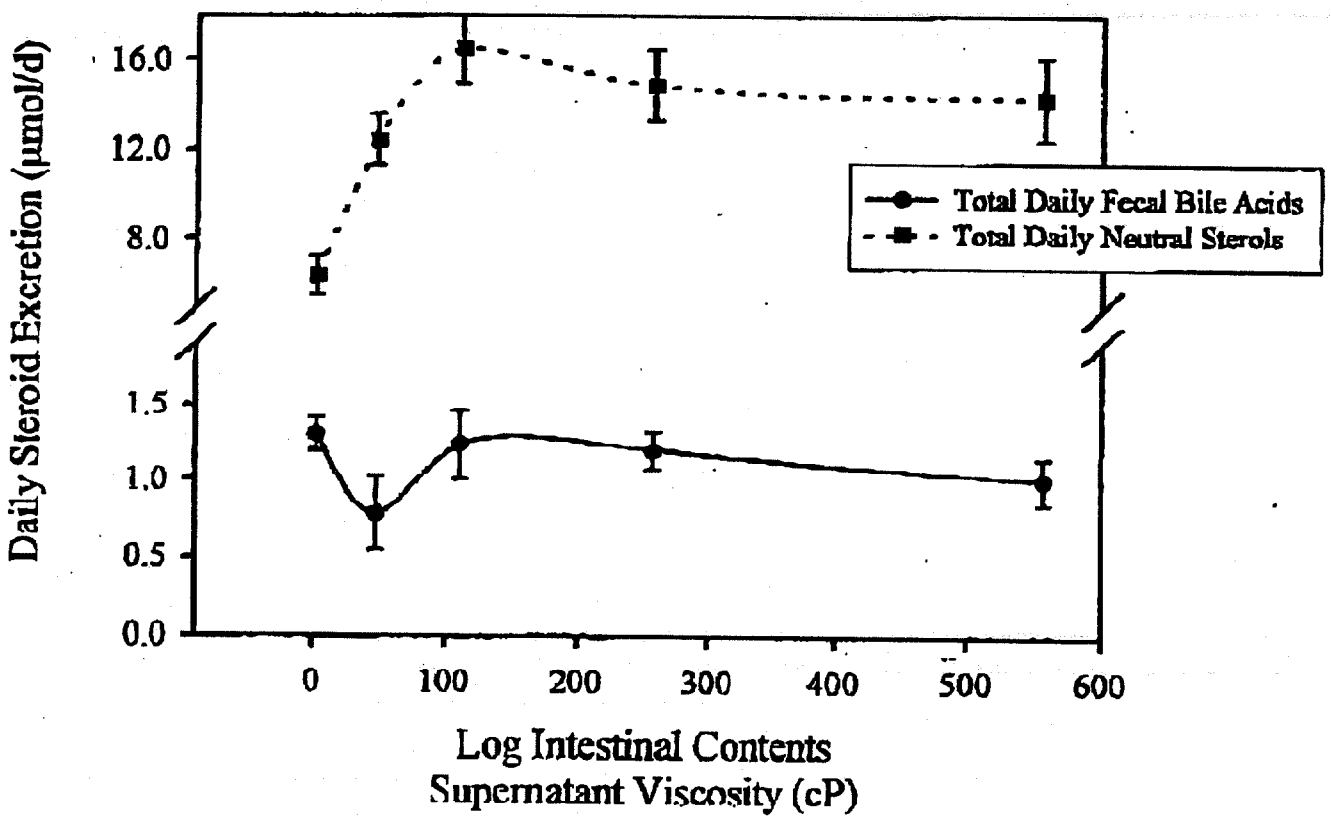
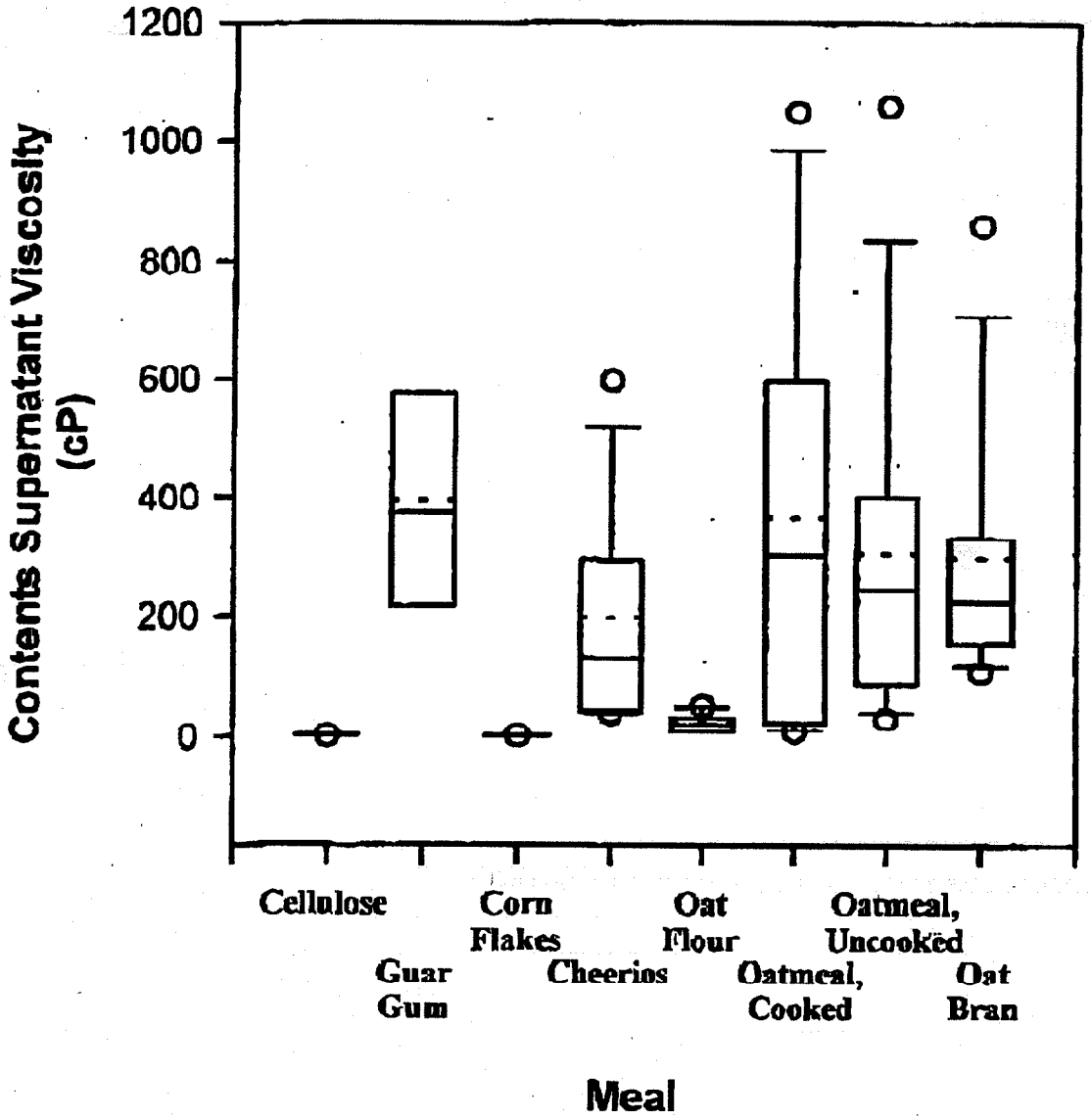


Figure 2
Intestinal Contents Viscosity of Rats Fed Meals of Breakfast Cereals



Notes For Figure 2

The data are presented as box plots because of lack of equal variance and deviation from a normal distribution. The solid line within each of the boxes of the box plots are the medians, wheress the dashed lines are the means The top and bottom of the boxes are the 25th and 75th percentiles of the data, and the top and bottom of the bars represent 10th and 90th percentiles. The circles outside of the bars are datapoints that fall outside the 10th to 90th percent distribution.

The rats were fasted overnight then fed their meals and killed 2-3 hours later The amount of cereal presented to the rats was 1/10th their serving size, as listed on the container. The breakfast cereals had some sugar added for palatability and some water as well. The AIN-76 diets (either cellulose or guar) were fed dry with no added sugar (the diets already contain some sugar). Since corn flakes had virtually no viscosity, the sugar clearly had no effect on viscosity. Most rats consumed the entire meal and all rats consumed most of their meal.

The viscosity values are underestimated for the oat bran group and, to a much lesser extent uncooked oatmeal group, as three samples for oat bran and one for uncooked oatmeal were too viscous to get a reading on our equipment.