

*trans* fat on LDL-C and CHD risk for the science section or the regulatory impact section, the basic conclusion about those effects is the same. That is, both *trans* fatty acids and saturated fatty acids raise LDL-C levels, a major risk factor for CHD risk. FDA did state in the review of the science in the 1999 proposal (64 FR 62746 at 62753) that the available studies did not provide a definitive answer about whether *trans* fat has an effect on LDL-C and CHD risk equivalent to saturated fat on a gram-for-gram basis. However, as stated previously in both this section and section IV of this document, to overcome the difficulties in interpreting individual intervention studies, in the November 1999 proposal FDA used regression equations based on a meta-analysis of intervention trials to quantitatively estimate the relationship between *trans* fat and LDL (Refs. 62, 65, and 69) in its calculation of the health benefits of *trans* fat labeling (64 FR 62746 at 62768–62770). The regression equations do predict a very similar increase in LDL-C with each one percent of energy increase in either saturated fat or *trans* fat. The regression equations used by FDA in this document and in the November 1999 proposal are appropriate for purposes of making a quantitative estimate of the health benefits as part of an economic analysis and are consistent with newer regression equations in a study published in 2001 (Ref. 130).

As previously described in this section and in section IV of this document, although FDA did not place primary reliance upon the relationships among *trans* fat intakes and adverse effects on HDL-C and CHD risk in deciding that nutrition labeling was warranted, FDA also recognizes this possible relationship, so concerns about possible adverse effects cannot be ignored. Therefore, we used changes in both HDL-C and LDL-C as a second method to quantify the effects of *trans* fat intake on CHD risk, with the noted qualification that the primary basis for the rule was the effect of *trans* fat on LDL-C (64 FR 62746 at 62769). As discussed in section V of this document, because of chemical and physiologic distinctions between saturated and *trans* fats, the agency has reconsidered the position that the two fatty acids should be declared as one combined entity. Declaration of the amount of *trans* fat on a separate line from saturated fat on the nutrition label is consistent with the possibility that the health benefits of *trans* fat labeling may be due to changes in LDL-C alone (Method 1), or to

changes in both LDL-C and HDL-C (Method 2).

In response to the comment about relative risk in the prospective studies, FDA acknowledges that relative risk estimates in prospective studies will depend on the base risk used for comparisons and this dependence on base risk may result in inaccuracies when the relative risk is related to the absolute risk in other studies or in the general population. However, FDA does not agree that this difference would change the basic conclusion of the prospective studies, that the CHD risk associated with *trans* fat in the prospective studies is much greater than the CHD risk expected due to either Method 1 (LDL-C) or Method 2 (LDL-C and HDL-C). In the 14-year followup of the Nurses Health Study (Ref. 38), the increased risk of CHD associated with *trans* fat intake compared with carbohydrate intake was more than ten times the increased risk for the same amount of saturated fat compared with carbohydrate. This comparison between *trans* fat and saturated fat was in contrast to the prediction based on Method 1 (LDL-C) or Method 2 (LDL-C and HDL-C). In Method 1, *trans* fat would be predicted to be associated with about the same increased risk as saturated fat, and in Method 2, *trans* fat would be predicted to be associated with about twice as much increased risk as saturated fat, comparing both with carbohydrate. This comparison was within a single study, so the difference between the results of this study and what would have been expected due to Method 1 or 2 cannot be attributed to any differences in baseline risk between studies. Moreover, although participants in large prospective studies have different baseline risks of CHD, the increased risk associated with known risk factors is often reasonably consistent across many of the studies. For example, the increased CHD risk associated with saturated fat for female nurses from 1980 to 1994 (Ref. 38) was quite similar to that for male employees of Western Electric Co. from 1958 to 1976 (Ref. 67) (64 FR 62746 at 62771). The changes in CHD risk associated with total cholesterol and HDL-C for male physicians from 1982 to 1987 was comparable to that for men and women from Framingham, MA in the 1970s (Ref. 131).

A meta-analysis of the relative risk of CHD associated with *trans* fat intake was recently published (Ref. 102). The meta-analysis used the results of prospective observational studies in four cohorts: Women in the United States, men in the United States, men in Finland, and men in the Netherlands.

The results showed a pooled variance-weighted relative risk of 1.25 (95 percent confidence interval 1.11 to 1.40) for CHD associated with 2 percent of energy intake from *trans* fat. For 0.1 percent of energy intake from *trans* fat, the meta-analysis results would predict a relative risk of 1.0112 (confidence interval 1.0052 to 1.0170). That is, for 0.1 percent of energy intake from *trans* fat, the increase in CHD risk would be 1.12 percent (confidence interval 0.52 to 1.70 percent). In comparison, the largest change in CHD risk shown in table 9, associated with 0.1 percent of energy intake from *trans* fat, is 0.162 percent using Method 1 and 0.292 percent using Method 2. Thus, the increase in CHD risk for 0.1 percent of energy intake from *trans* fat based on a meta-analysis of prospective studies is larger than the associated CHD risk estimated using either Method 1, LDL-C or Method 2, LDL-C and HDL-C. (The calculation of relative risk at different levels of *trans* fat intake is based on taking the natural logarithm. For 2 percent of energy intake from *trans* fat, the estimated relative risk was 1.25. The coefficient in the logistic regression is the natural logarithm of 1.25 = 0.223;  $0.223/2 = 0.1116$ , the coefficient for 1 percent of energy from *trans* fat;  $0.1116 \times 0.1 = 0.0112$ , the coefficient for 0.1 percent of energy from *trans* fat; the antilogarithm of 0.0112 = 1.0112, the relative risk associated with 0.1 percent of energy from *trans* fat.)

Thus, FDA disagrees with the comment about relative risk in the prospective studies, and maintains that the prospective studies do suggest that there may be additional mechanisms, besides changes in LDL-C and HDL-C, by which *trans* fat contributes to CHD risk. However, as discussed previously in this section, and in the November 1999 proposal (64 FR 62746 at 62771), FDA did not use the results of the prospective studies in its quantitative estimate of the health benefits of *trans* fat labeling. The sole use of the prospective studies was to suggest that there may be additional mechanisms by which *trans* fat contributes to CHD. The prospective studies thus indicate the direction of the uncertainty in the benefits estimate: That the actual benefits may be higher than the benefits estimated using Methods 1 and 2.

In response to the comments about the Ascherio et al. regression equation as discussed in the IOM/NAS report (Ref. 140), FDA notes that according to the NEJM, all submissions to the journal are peer-reviewed before publication. The comments did not cite any published articles questioning the 1999 Ascherio et al. paper (Ref. 83), and did