

saturated fats on a gram-for-gram basis. However, FDA also stated that the studies that compared a saturated fat diet with a diet in which some of the saturated fat was replaced with *trans* fat showed that *trans* fat, like saturated fat, increases LDL-C.

For purposes of its regulatory impact analysis in the proposal, FDA needed a basis for quantifying its estimates of the compliance costs and benefits associated with given changes in *trans* fat intakes and the associated changes in CHD risk. The available evidence always presents some uncertainty for these types of analyses, as there is with other inputs into regulatory decisions. Given these caveats, FDA, in order to develop the tools required for a quantitative evaluation of benefits and costs, reviewed a meta analysis of five intervention trials that included six levels of *trans* fat intakes (Refs. 62 and 69). Using multiple regression to statistically control for differences in other fatty acids between *trans*-enriched diets and reference diets, the authors projected linear increases in LDL-C as a function of level of increasing *trans* fat intake. According to the regression equations, each additional percent of energy from *trans* fat, when substituted for the same percent of calories from *cis*-monounsaturated fatty acids, was predicted to increase LDL-C by 1.5 mg/dL. This relationship was then used as the basis for estimating the benefits and costs of the proposed rule and not for purposes of establishing whether there is a gram-for-gram relationship between *trans* and saturated fatty acids on LDL-C levels and CHD risk. FDA notes that, in rulemaking to implement the 1990 amendments, the agency also found it necessary to use coefficients derived from regression equations to estimate the benefits and costs of various regulations (56 FR 60856, November 27, 1991; 58 FR 2927, January 6, 1993). In one such analysis, FDA used the equation of Hegsted and Keys to predict how changes in total serum cholesterol would be affected by projected changes in saturated fat intake (56 FR 60856 at 60869, November 27, 1991). Because the Hegsted and Keys equations did not include coefficients for *trans* fat or information on components of total cholesterol (e.g., LDL-C), FDA found it necessary to find regression equations that included *trans* fat intakes and LDL-C levels. The equations of Katan et al. and Zock et al. (Refs. 62 and 69), together with the equations of Mensink and Katan (Ref. 65), which summarized the results of 27 clinical trials, were available to meet this need for a quantitative basis on which to estimate

the benefits and costs of the proposed rule.

In estimating the benefits and costs, FDA also recognized that the type of macronutrient substituted for *trans* fat in the diet would affect the magnitude and nature of the changes in LDL-C in response to decreases in *trans* fatty acid intakes. Thus, FDA also estimated how the benefits and costs would be altered if saturated fat, *cis*-polyunsaturated fat or carbohydrate, rather than *cis*-monounsaturated fat, were used to replace some of the *trans* fat in the diet. In this analysis an intermediate step in the calculation showed that when saturated fat was substituted for *cis*-monounsaturated fat, LDL-C was raised by 1.52 mg/dL, an amount similar to that found when *trans* fat was substituted for *cis*-monounsaturated fat (1.50 mg/dL).

Regardless of whether FDA reviewed the effects of saturated fat and *trans* fat on LDL-C and CHD risk for the science section or the regulatory impact section, the 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. Consumers need to minimize their intakes of both types of fatty acids within a moderate fat intake to implement dietary guidelines for healthful diets. These conclusions are consistent with those reached independently by expert panels (Refs. 87, 89, 90 and 91).

(Comment 10) Many comments addressed the issue of the potential adverse effects of *trans* fat on HDL-C levels. Some comments suggested that *trans* fat has more adverse health effects than saturated fat because *trans* fat, in addition to raising LDL-C, also lowers HDL-C, the so-called "good" cholesterol, whereas saturated fat raises HDL-C. Some comments noted that *trans* fat raises the LDL/HDL ratio approximately twice as much as saturated fat. Other comments stated that, in the prospective studies, the risk of CHD associated with *trans* fat intake was much greater than the risk associated with saturated fat, and much greater than would be predicted based on the effect on serum lipids. In contrast, one comment stated that it is premature to conclude that *trans* fat intake lowers HDL-C because many intervention studies showed that *trans* fat intake causes only a small decrease or has no effect on HDL-C.

Based on the recommendations of the 1993 NCEP Expert Panel (Ref. 5), in the November 1999 proposal, FDA concluded that an examination of the effects of *trans* fatty acids on serum LDL-C would provide the strongest

evidence, and should be the primary criterion, to evaluate whether *trans* fatty acids influence CHD risk. In the November 1999 proposal, FDA tentatively concluded that the available evidence demonstrated that under conditions of use in the United States, consumption of *trans* fatty acids contributes to increased serum LDL-C levels, which increases the risk of CHD. The evidence for this relationship alone was sufficient for the agency to tentatively conclude that addressing *trans* fatty acids in nutrition labeling is important to public health.

FDA's review of the intervention trials showed that HDL-C decreased when *trans* fats replaced saturated fats. Further, Federal Government advisory groups (Refs. 88 through 90, and 140) and an advisory group of health professionals (Ref. 91) have stated that substitution of *trans* fat for saturated fat lowers HDL-C.

To date, lowered HDL-C levels have been shown to be a useful predictor of heart disease risk because of its correlation with CHD risk. However, it is not known whether lowering HDL-C is related to CHD risk in a cause and effect manner. Until this relationship is confirmed by appropriate study designs, the use of HDL-C as a surrogate biomarker for CHD risk must be done with caution and clear recognition of the uncertainty surrounding this use. For example, FDA notes that the NCEP 2001 Report (Ref. 89) makes several statements that both recognize and qualify the relationship between *trans* fatty acids, HDL-C, and CHD risk. While the NCEP Report states that a low HDL-C level is strongly and inversely associated with risk for CHD, the NCEP Report also states that, because of the association of low HDL levels with other atherogenic factors, a low HDL-C is not as strongly independent in its prediction as suggested by usual multivariate analysis.

Therefore, while 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 (64 FR 62746 at 62798 to 62821). For this reason, FDA included information on the effects of *trans* fatty acids on HDL-C levels when reviewing the available human studies in the science review section. Additionally, because of the possibility of an adverse effect on HDL-C levels from *trans* fat intake and a correlation between such an effect with CHD risk, the possible impact on HDL-C levels from *trans* fat