

(Comment 7) Other comments suggested that the study populations were not representative of the U.S. population. For example, one comment said that the intervention studies included individuals at high risk with serum cholesterol levels greater than (>) 320 milligrams (mg)/deciliter (dL) or LDL-C > 130 mg/dL. Another comment stated that the agency failed to reflect that relative risk will depend on the base risk of the population used for comparisons with the U.S. general population.

FDA disagrees with these comments. Of the 512 subjects included in the dietary intervention studies cited in the November 1999 proposal, 48 percent of the dietary intervention population had an LDL-C level of 100 to 120 mg/dL that is categorized as near or above optimal level according to the NCEP lipid classification scheme (Ref. 89). Thirty-eight percent had an LDL-C of 130 to 159 mg/dL, categorized as borderline high; and 14 percent had a LDL-C of greater than or equal to (\geq) 160 mg/dL, categorized as high. Only 5 percent of the participants had a low HDL-C level, < 40 mg/dL; and another 7 percent had a high HDL-C level, \geq 60 mg/dL. Most (88 percent) had mean HDL-C levels in the range of 41 to 59 mg/dL. Also, 73 percent of the population was in the age group where the CHD risk is lower, e.g., men < 45 years of age and women < 55 years of age. The study populations were described as participants who had normal cardiac, kidney and liver function, and were not taking medications that affect lipid levels. Many participants had near or optimal LDL-C levels and most had HDL-C levels that were neither high nor low by the NCEP criteria. The data that FDA relied on included a dietary intervention population that is representative of the U.S. general population.

(Comment 8) Some comments suggested that the test products were not representative of available commercial products in the U.S. marketplace. One comment suggested that several studies were designed to study the effects of different food oil sources and not designed to specifically study the effect of *trans* fat on blood lipid levels.

FDA disagrees with these comments. In general, the test products used in studies done by U.S. research groups were either commercially available products or were produced specifically for a study by U.S. manufacturers using oil sources commonly used in the U.S. market (Refs. 12 through 15, 34, and 82). However, regardless of whether studies used products typical of those

commercially available in other countries, products commercially available in the United States, or products developed specifically for the study at hand, results were generally consistent across all these studies and consistent with the larger body of evidence that included studies done in Europe and with European oils. That is, there was consistency across studies in finding that higher intakes of *trans* fat resulted in increased levels of LDL-C and, therefore, in increased risk of CHD. Moreover, the observational studies in U.S. populations, where participants were consuming products commercially available in the U.S. marketplace, also consistently showed that higher intakes of *trans* fat were associated with adverse effects on CHD risk (Refs. 19, 21, and 38).

FDA also recognizes that the intervention studies were designed with a variety of objectives in mind. Some were designed to compare two different sources of hydrogenated oils (e.g., Refs. 9, 14, 15, and 36). Many were designed to compare the effects of different types of fatty acids by varying the source oils to achieve the desired fatty acid types and levels (e.g., Refs. 7, 8, 10, 11 through 13, and 34). The study designs also varied significantly in how they identified controls for the comparisons of interest. Despite these differences in objectives and study design, the general consistency across studies in finding that *trans* intakes are adversely related to CHD risk provides evidence that the relationship is likely real and not simply an artifact of a particular type of study design (Ref. 94).

Thus, most of the intervention trials provide enough information about test products, study population, and study diets to evaluate their relevance to the U.S. general population. The wide range of *trans* fatty acid intakes, products, and population characteristics in these studies overlaps with those found for U.S. consumers in the general population. Important, however, is that there is remarkable consistency across the intervention studies, regardless of population, products and diets used, in finding that higher intakes of *trans* fatty acids are associated with increased levels of serum LDL-C, a major risk factor for CHD. Thus, the available intervention studies show consistent results across a broad range of use conditions and population characteristics. FDA, therefore, disagrees with comments that suggest that the test products used in intervention studies are not applicable to the U.S. marketplace, or the study designs are not applicable to evaluating

the relationship of *trans* fat to CHD risk in the U.S. population.

(Comment 9) Many comments questioned whether the scientific evidence shows that the physiological effects of *trans* fat on CHD risk are equivalent to, greater than, or less than those of saturated fat on a gram-for-gram basis. Some comments noted that the intervention studies show that the increase in LDL-C levels associated with *trans* fat is greater than that from unsaturated fats but less than that from saturated fat. Some comments noted that in the review of science for the November 1999 proposal, FDA concluded that the available studies do not provide a definitive answer to the question of whether *trans* fatty acids have an effect on LDL-C and CHD risk equivalent to saturated fats on a gram-for-gram basis, but in the preliminary regulatory impact analysis, FDA estimated that the effects of saturated and *trans* fatty acids on LDL-C levels are about equivalent.

FDA notes that the intervention studies demonstrate that the net physiologic effect of a particular fatty acid or category of fatty acids is dependent upon the composition of both the intervention diet and the comparison diet. In the dietary intervention research reviewed, the study investigators used a variety of study designs to assess the effect of a defined quantity of *trans* fatty acids (provided by food sources of hydrogenated oil) on levels of serum or plasma lipids. The best study designs controlled the variation in the ranges of protein, fat, cholesterol, and carbohydrate with particular attention given to the fatty acids. The effect of *trans* fat study diets were compared by replacement with food sources of: (1) *Cis*-unsaturated fatty acids, (2) monounsaturated (oleic) fatty acids, and (3) saturated fatty acids. As FDA stated in the November 1999 proposal (64 FR 62745 at 62750), the intervention study data showed the following: (1) *Trans* fatty acids increased LDL-C in comparison with *cis*-polyunsaturated fatty acids (Refs. 8, 13, 15, and 82); (2) *trans* fatty acids increased LDL-C levels in comparison with *cis*-monounsaturated fatty acids (Refs. 7, 11 and 12); and (3) *trans* fatty acids increased LDL-C, or there was no significant difference, in comparison with saturated fatty acids (Refs. 7 through 12). Based on these results, FDA concluded in the science review section of the November 1999 proposal that the available studies do not provide a definitive answer to the question of whether *trans* fatty acids have an effect on LDL-C and CHD risk equivalent to