

consumers and those who need to lower their LDL-C level minimize their intakes of *trans* fat to reduce their risk of CHD. For example, the IOM/NAS noted "a positive linear trend between *trans* fatty acid intake and total and LDL-C concentrations, and therefore, increased risk of CHD, thus suggesting an upper limit of zero" (Ref. 90). However, they further stated that, because *trans* fatty acids are unavoidable in ordinary diets, a complete avoidance of these fats is not possible without extraordinary changes in patterns of dietary intake. Such extraordinary adjustments may introduce other undesirable effects (e.g., elimination of foods such as dairy products and meats that contain *trans* fatty acids may result in inadequate intakes of protein and certain micronutrients). For these reasons, the IOM/NAS recommended that *trans* fatty acid consumption be as low as possible while consuming a nutritionally adequate diet. In response to the comments about the scientific validity of an article used in the IOM/NAS report, FDA notes that the paper by Ascherio and coworkers (Ref. 83) is not the only information that the IOM/NAS relied on to conclude that *trans* fatty acid consumption should be as low as possible relative to CHD risk. Moreover, FDA did not find the LDL/HDL cholesterol ratio used in the Ascherio et al. analysis to be a useful endpoint for purposes of the *trans* fatty acid rule-making (see Comment 10). Additionally, FDA's independent evaluation of the scientific evidence concluded that there is consistency in finding adverse effects of *trans* fat on risk of CHD. Therefore, even though the independent reviews of FDA and the other expert panels differed to some degree in how they used the available scientific evidence, the resultant consistency of the conclusions across these reviews provides strong credence to the finding that *trans* fatty acid consumption increases CHD risk via increases in LDL-C.

In summary, based on the consistent results across a number of the most persuasive types of study designs (i.e., intervention trials and prospective cohort studies) that were conducted using a range of test conditions and across different geographical regions and populations, the agency now agrees with the comments that stated that the available evidence for an adverse relationship between *trans* fat intakes and CHD risk is strong. FDA also finds the results from the large prospective cohort studies among free-living U.S. population groups to be persuasive

evidence that the *trans* fat intakes associated with U.S. dietary patterns can have a significant adverse effect on CHD risk for U.S. consumers. The scientific agreement for this relationship among the various expert groups and consensus among these expert groups in recommending that U.S. consumers limit their intakes of saturated and *trans* fats now provide further evidence of the strength of the science and the public health importance of lowering *trans* fat intakes for U.S. consumers. Therefore, the comments do not persuade FDA to change its position in the proposed rule that labeling of *trans* fatty acids is warranted based on: (1) The scientific evidence; and (2) the public health importance of the guidelines recommending that consumers limit their intakes of both of the LDL-C-raising fats: *trans* and saturated fats. Thus, FDA concludes that its tentative conclusion in the proposed rule 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" (64 FR 62746 at 62754) is no longer tentative. FDA continues to find the overall weight of scientific evidence in support of this conclusion to be sufficiently compelling to now warrant *trans* fatty acid labeling.

(Comment 4) Several comments stated that a new observational study by van de Vijver et al., "Association between *trans* fatty acid intake and cardiovascular risk factors in Europe: The *trans*FAIR Study" (Ref. 93) showed no association between average total *trans* fat intake in Europe and LDL-C or HDL-C so that average *trans* fat intake in the United States is probably not detrimental to human health.

FDA disagrees with the comments. The *trans*FAIR study had a cross-sectional design, measuring *trans* fatty acid intake and serum lipids in 327 men and 299 women, ages 50 to 65 years, in 8 European countries from approximately 1997 to 1999. The study reported no statistically significant association between total *trans* fat intake and serum LDL-C. The habitual intake of *trans* fat was estimated to be about 2 g/day (e.g., approximately 1 percent of calories).

FDA notes that cross-sectional designs, such as the one used by van de Vijver et al., are relatively weak designs for showing associations between diet and serum lipids (Ref. 93). As an observational study, they are generally considered to be less persuasive than intervention trials. Moreover, compared with other types of observational studies (e.g., prospective (cohort) observational studies and retrospective (case-control)

studies), they are considered particularly weak. Considering the weaknesses of the cross-sectional design used in the *trans*FAIR study compared with the much larger body of evidence from more persuasive types of studies (i.e., intervention trials and prospective observational studies) that consistently demonstrate an adverse effect of *trans* fat intakes on LDL-C, FDA does not find the *trans*FAIR study to be sufficiently compelling to override the overall weight of the scientific evidence reviewed in the November 1999 proposal or to override the independent conclusions of recent expert panels convened by the Federal Government (Refs. 87 and 89), the IOM/NAS (Ref. 90), and the AHA (Ref. 91).

For the reasons cited previously, FDA disagrees with the comments that a lack of association between *trans* fat intake and serum lipids in the European *trans*FAIR study indicates that average *trans* fat intake in the United States is probably not detrimental to human health.

(Comment 5) Many comments emphasized the inadequacies in the assessment of intakes of *trans* fatty acids by the U.S. population and noted that the current data are insufficient in regard to the *trans* fatty acid content of foods. One comment noted that USDA's data for the *trans* fatty acid content of foods are limited to a few foods with a small number of samples. Thus, the comment concluded that extrapolation of *trans* fatty acid content from a few foods must be used to estimate the content of *trans* fat in the large number of foods that make up the total diets of the U.S. population. This extrapolation results in intake estimate errors with unknown effects. Some comments assert that the data are an over-estimate of the U.S. population's *trans* fatty acid intake and other comments assert that the data are an under-estimate.

FDA agrees that estimates of dietary intakes of *trans* fat, as with all intake estimates based on participant reports and limitations in compositional data bases, are subject to multiple sources of error. In the November 1999 proposal, the agency reviewed intake estimates from three different types of data: (1) National food consumption survey, (2) national disappearance data, and (3) observational studies done in U.S. population groups. By examining results from multiple methods of estimating intakes, the agency was able to assess some, but not all, of the uncertainties in current intake estimates. In discussing these data, FDA noted the very limited composition data available for the *trans* fatty acid composition of foods and the difficulties in determining the accuracy