considers this study to offer only limited evidence of the allergenicity of FD&C Yellow No. 6 because the report does not give complete details of the design of the study.

Sweatman et al. in 1986, published a case report of an 8-year-old girl with oro-facial granulomatosis (Ref. 9). This disease consists of swelling of the lips and face, frequently with vertical fissures in the lips and oral mucosal abnormalities. Oro-facial granulomatosis has been associated with sarcoidosis and Crohn's disease, but these diseases were ruled out in this case by clinical pathology tests. However, a double-blind challenge test produced a severe reaction to sunset yellow and carmoisine, another azo dye. The authors concluded that while these additives were clearly a cause of her condition, it was likely that other foods were also involved.

A 1986 study by Supramaniam and Warner focused on food additive intolerance in a group of children with a history of angioedema or urticaria (Ref. 10). The children underwent double-blind, placebo-controlled challenge testing with several food and color additives including sunset yellow. The additives or placebo were given in 4-hour intervals, and examinations for skin reactions, temperature changes, pulse and respiration rates, and peak expiratory flow rate were done at 15-minute intervals. A reaction was judged positive if either urticaria or angioedema occurred. Of the 36 children who were challenged with sunset yellow, 10 reacted positively. Although limited information is given in this paper, the study appears to have been well-conducted and provides support for the existence of hypersensitivity to FD&C Yellow No. 6 based on the percentages of children who reacted to sunset yellow. The investigators did not specify the amounts of the additives used in the testing protocol, only that smaller quantities of the additives were used than might be ingested in an estimated maximum daily intake.

In 1987, Murdoch et al. studied 24 patients with urticaria who were in remission on an additive-free diet by subjecting them to placebo-controlled, double-blind outpatient challenge testing with encapsulated food additives (Ref. 11). Three of the subjects gave positive responses to at least two separate challenges to azo dyes, with negative responses after placebo. These three subjects then underwent single-blind challenge testing in a hospital. One of the three subjects reacted to sunset yellow both in outpatient and hospital challenge tests. The subject experienced erythema and pruritus, with significant increases in plasma histamine levels in the hospital testing. The agency concludes that this study offers only limited evidence of the allergenicity of FD&C Yellow No. 6 because the hospital testing was only single-blinded and not placebo-controlled.

In 1989, Gross et al. reported the case of a physician who experienced severe abdominal pain and urticaria which required four hospitalizations within a 2-year period (Ref. 12). Small intestinal biopsies revealed chronic inflammation and eosinophils. FD&C Yellow No. 6 was the one common additive in all the foods and drugs that were suspected of causing the problem. The patient was challenged with FD&C Yellow No. 6 (using 8 milligram capsules) and encapsulated brown sugar as the placebo in a single-blind test. One capsule was given twice a day for 4 days. The patient developed abdominal cramps, hives, and nervousness following the administration of the FD&C Yellow No. 6, which was given first, but not after placebo. The patient subsequently underwent a placebo-controlled, double-blind challenge with the capsules given twice a day for 5 days. Placebo was administered first with no effect. However, severe abdominal cramps and marked fatigue occurred when FD&C Yellow No. 6 was administered. The authors concluded that the patient was suffering from allergic gastroenteritis from FD&C Yellow No. 6. This study was adequately conducted, and the results clearly document a case of adverse reaction to FD&C Yellow No. 6.

B. FDA's Tentative Conclusion Concerning Allergenicity of FD&C Yellow No. 6

In evaluating the reports described above, the agency recognizes that there are deficiencies in the conduct of some of the clinical studies (Ref. 13). However, in spite of the limitations of the studies, the agency tentatively concludes that the available evidence supports an association of FD&C Yellow No. 6 with allergic-type responses in susceptible individuals who may be exposed to this color additive in food, drugs, and cosmetics containing it. Therefore, under section 721(b)(3) of the act, the agency tentatively concludes that the label declaration of FD&C Yellow No. 6 is necessary as a condition of use to ensure a reasonable certainty of no harm from the prescribed use of the color additive for those susceptible individuals.

As discussed previously, § 101.22(k)(1) requires the label declaration of certifiable color additives, including FD&C Yellow No. 6, added to foods, while § 101.22(k)(3) exempts butter, cheese, or ice cream from this requirement unless the label declaration is required for safe conditions of use under part 73 or 74 (21 CFR part 73 or 74). Therefore, the agency is proposing to require that the labels of butter, cheese, and ice cream disclose when FD&C Yellow No. 6 is present in the food. Furthermore, the agency is proposing that drug products administered to mucous membranes that contain this color additive declare its presence in their labeling. This labeling requirement, if adopted, will serve to inform the public of the presence of FD&C Yellow No. 6 in these food and drug products and thus enable susceptible individuals to avoid it. The knowledge acquired through labeling of consumer products may also be of assistance when susceptible individuals patronize places, such as restaurants, where foods would not ordinarily be labeled.

Label declaration of specific color additives in cosmetics has been required since May 31, 1976. Thus, no action is required for cosmetics.

III. Label Declaration

A. Food

Section 721(b)(3) of the act provides that regulations for the listing of a color additive shall ''prescribe the conditions under which such additive may be safely employed for such use or uses (including but not limited to,* * * and directions or other labeling or packaging requirements for such additive).'' As reviewed above in this document, FD&C Yellow No. 6 has been reported to be associated with allergic-type responses in humans. Thus, the agency tentatively finds that the requirement for label declaration of the color additive in butter, cheese, or ice cream, which are currently exempt from such declaration under section 403(k) of the act, is justified.

Consumers who may be allergic to FD&C Yellow No. 6 are likely to be selective of the types of foods that they use and to read ingredient listings on food labels to avoid the allergic-type reactions to the color additive. The label declaration of FD&C Yellow No. 6 in human foods, except butter, cheese, and ice cream, is already required under § 101.22(k)(1). Accordingly, a label declaration of the presence of FD&C Yellow No. 6 in butter, cheese, and ice cream, whether added as the straight color additive, a mixture, or a lake, will enable persons who may be sensitive to FD&C Yellow No. 6 to avoid unwitting