increased; GI and central nervous system (CNS) reactions were similar; and other reactions decreased.(5)

The relevant literature shows that naproxen and other NSAID's have adverse fetal effects when used during pregnancy. A newborn delivered 8 hours after his mother ingested an overdose of 5 grams of naproxen developed severe hyponatremia (low blood sodium) and water retention with indications of cerebral irritation and paralytic ileus. It was tentatively diagnosed that naproxen adversely affected renal function. Complications were reported in three newborns after maternal naproxen treatment to prevent premature labor. One newborn died, and the autopsy showed a brain hemorrhage, multiple gastric ulcers, extensive GI bleeding, and a cardiovascular birth defect that is a known adverse effect of NSAID's. A 7-day-old breast-fed infant boy developed symptoms associated with naproxen toxicity after his mother was treated with 1 g naproxen and 800 mg of antibiotic for 3 days.(5)

C. Level for Regulation

The Commission is issuing a rule that requires special packaging for OTC naproxen products containing the equivalent of 250 mg or more naproxen per retail package. This level is based on established guidelines for medical treatment following ingestion of NSAID's. It is also based on a known toxic dose of naproxen, reduced by a safety factor to account for biologic variability. (5 and 10)

The precise toxic level of naproxen in humans is unknown. However, guidelines established for pediatric NSAID overdose suggest medical treatment for young children who ingest five times the maximum single therapeutic dose. Therefore, the dose of naproxen requiring medical intervention would be 5 mg/kg (the maximum single therapeutic dose) times five, or 25 mg/kg. In a 10-kg child, this is equivalent to 250 mg of naproxen, or one and one-quarter OTC tablets. (5 and 10)

The same level results when calculated using a different approach. When treatment information for poisonings is unavailable, the staff typically uses a known toxic dose divided by a safety factor of 10 to determine the level for regulation. Applying this factor to the 250 mg/kg dose of naproxen that caused life-threatening acidosis in a 15-year-old girl also results in a level of 25 mg/kg, or 250 mg in a 10-kg child. (5 and 10)

The Commission emphasizes that the 250 mg level applies to the total amount of the product sold at retail in a single package, regardless of whether the contents of the package are loose or also packaged in non child-resistant envelopes or strip packages. In administering the PPPA regulations for acetaminophen, iron-containing preparations and ibuprofen, the Commission has encountered instances in which product manufacturers package one or two tablets in individual envelopes for sale to consumers seeking medication for immediate use. Because each envelope is an individual retail unit and contains less than the amount of ibuprofen or acetaminophen subject to regulation, the envelopes need not be child-resistant.

However, the Commission has also encountered instances in which repackagers have packaged multiple non child-resistant envelopes of acetaminophen, iron, or ibuprofen in outer blister packs or clamshell packages that contain a total quantity of these products in excess of the regulatory minimum, but that are also not child-resistant. We note that the regulatory minimum contained in a ''single package'' refers to the total contents of the retail package, not the contents of each individual envelope. To avoid future confusion on this issue, this regulation refers to the contents of the ''retail package'' to clarify that whether a product requires child-resistant packaging is based on the total amount of naproxen packaged for sale at retail.

D. Comments on the Proposed Rule

The Commission received four comments responding to the proposed rule. These came from the American Society of Health-System Pharmacists, the National Association of Pediatric Nurse Associates and Practitioners, and two groups of university students. All agreed that the Commission should require CR packaging for naproxen. In addition, the students argued for an effective date shorter than the 180-day period proposed by the Commission. One group of students advocated a 90-day effective date. The argument for the shorter date was that the companies with exclusive marketing rights are voluntarily using CR packaging now.

The Commission does not agree that a shorter effective date is necessary. In general, the PPPA requires at least 180 days before a regulation takes effect. 15 U.S.C. 1471n. As explained in section F below, the Commission does not believe that a shorter period is justified in this case.

E. Statutory Considerations

1. Hazard to Children

As noted above, the toxicity data concerning children's ingestion of naproxen sodium demonstrate that this compound can cause serious illness and injury to children. Moreover, the preparations are readily available to children.(5) The Commission concludes that a regulation is needed to ensure that products subject to the regulation will be placed in CR packaging by any new manufacturers. In addition, the regulation will enable the Commission to enforce the CR packaging requirement and ensure that effective CR packaging is used.

Pursuant to section 3(a) of the PPPA, 15 U.S.C. 1472(a), the Commission finds that the degree and nature of the hazard to children from ingesting naproxen is such that special packaging is required to protect children from serious illness. The Commission bases this finding on the toxic nature of these products, described above, and their accessibility to children in the home.

2. Technical Feasibility, Practicability, and Appropriateness

In issuing a standard for special packaging under the PPPA, the Commission is required to find that the special packaging is ''technically feasible, practicable, and appropriate.'' 15 U.S.C. 1472(a)(2). Technical feasibility may be found when technology exists or can be readily developed and implemented by the effective date to produce packaging that conforms to the standards. Practicability means that special packaging complying with the standards can utilize modern mass production and assembly line techniques. Packaging is appropriate when complying packaging will adequately protect the integrity of the substance and not interfere with its intended storage or use. (9)

The current marketers of OTC naproxen use packaging that not only is child resistant, but also is easier for adult consumers to open. Therefore, the Commission concludes that CR packaging for naproxen is technically feasible, practicable, and appropriate.

3. Other Considerations

In establishing a special packaging standard under the PPPA, the Commission must consider the following:

a. The reasonableness of the standard;

b. Available scientific, medical, and engineering data concerning special packaging and concerning childhood accidental ingestions, illness, and injury caused by household substances;