of safety. I believe he referenced that as few as four doses could be a severe problem. Can you comment on that?

Dr. FURMAN. I believe that you have reference to a study by a Danish investigator.

Senator HATCH. That is right.

Dr. FURMAN. Simonsen.

Senator HATCH. It is on page 3.

Dr. FURMAN. Oh, yes. This is interesting because Simonsen has reported a series of 30 patients; 30 deaths from drug abuse and, of these 30, some 15 were related to the use of propoxyphene. What Dr. Wolfe did not tell us is that, of these 15 propoxyphene-related deaths, 8 occurred in individuals who used a formulization which is peculiar to Scandinavia, a so-called slow-release or delayed-release propoxyphene product that contains twice the standard recommended dose of propoxyphene. So, if one were to take four of this sustained-release product, one would be, in effect, dosing oneself with eight 65-milligram capsules of propoxyphene hydrochloride. And, if the individual took a drink or two along with these and helped elute the propoxyphene from the sustained-release preparation, he would be in serious trouble, as were many of these patients.

One of these individuals killed himself with 8 of these sustained-release tablets, which means he took the equivalent of 16 doses of propoxyphene hydrochloride.

Senator HATCH. Is that the 65-milligram level?

Dr. FURMAN. Yes, sir. I should point out that we do not have such a formula. We have never had a formula of this sort anywhere in the world. The 15 patients in this publication included seven that were classified as drug addicts. In addition, four had taken alcohol and three had taken barbiturates along with the propoxyphene.

Senator HATCH. Well now, Dr. WOLFE stated, "The information that chronic use of Darvon leads to high blood levels of the toxic metabolite nor-propoxyphene has never been publicly acknowledged by Lilly." Could you please comment on this?

Dr. FURMAN. Nor-propoxyphene occurs in the liver within minutes of propoxyphene's reaching the bloodstream. In a constant-dose situation, the level of nor-propoxyphene rises to a plateau at which it remains, the amount excreted equaling the amount that is formed. Since it has a slightly longer half-life—that is, it is excreted more slowly—the concentrations of nor-propoxyphene attained in a chronic dose situation exceed, in many instances, those of propoxyphene.

Information on the metabolism of propoxyphene and the pharmaceutical activity of nor-propoxyphene has been developed mainly in the Lilly laboratories but has been confirmed, and this information has been published by both European and U.S. investigators.

The concern about nor-propoxyphene is based on its local anesthetic property, which might interfere with normal heart conduction.

In an experiment on anesthetized animals with electrodes inserted in proper portions of the heart, evidence of delayed conduction can be elicited.

In two abstracts submitted to the meetings of the Federated Societies, these studies were described. One of these abstracts, which was sent to FDA, indicated that propoxyphene and its principal metab-