

ELI LILLY AND Co.,
Indianapolis, Ind., January 30, 1979.

HON. GAYLORD NELSON,
Chairman, Select Committee on Small Business, U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: The information in this letter supplements Lilly's response to your inquiry of January 15, 1979, to Mr. Richard D. Wood. In responding to your inquiry, we provided information with my letter of January 26, and indicated with respect to item 1 that we would provide additional published and unpublished information promptly. The following is an addendum to the materials previously furnished in response to item 1.

The initial new drug application for Darvon (propoxyphene hydrochloride), submitted in March 1957, contains information about studies of cardiac function, as a part of the general pharmacologic effects of the drug. Anesthetized dogs given continuous intravenous infusions of propoxyphene until death had no pronounced changes in their ECGs (electrocardiograms), and it was concluded that the compound produced no deleterious cardiac effects. Minor ECG changes were observed when the animals were near death.

Additional cardiac studies were reported in the IND (Investigational New Drug) filings for Darvocet and the NDA for Darvon-N in 1968. In the Darvocet Ind, a study in anesthetized cats given 5 mg/kg I.V. showed some ECG changes; at 0.5 mg/kg these changes were not noted. In the Darvon-N NDA, a similar study in anesthetized cats given the same dose of propoxyphene I.V. revealed no significant effects on cardiac rhythm.

In addition, no significant effects on cardiac rhythm were seen in the ECG's of conscious dogs given 40 mg/kg orally.

Studies in progress have shown that the prolongation of the PR interval produced by intravenous administration of propoxyphene hydrochloride in conscious dogs is not blocked by the anticholinergic drug atropine or the opiate antagonist naloxone. Preliminary experiments were also initiated to explore the therapeutic potential of propoxyphene and norpropoxyphene as antidysrhythmic agents. The compounds are weakly active and no further studies are planned to explore this activity.

The foregoing information completes our response to question number 1.

Very truly yours,

EDGAR G. DAVIS,
Vice President, Corporate Affairs.

RESPONSE TO ITEM No. 1

The following discussion of the pharmacology and toxicology of propoxyphene and norpropoxyphene describes the unpublished information Lilly has about studies of the cardiac effects of propoxyphene and norpropoxyphene in humans and animals.

In man propoxyphene is rapidly metabolized to norpropoxyphene, the principal metabolite. Norpropoxyphene has little analgesic ("opiod") activity (1/2 to 1/40 that of propoxyphene, depending on the assay method utilized), while its local anesthetic activity is two to three times that of the parent compound. The "opiod" effects are antagonized by agents such as naloxone, whereas local anesthetic effects are not. At certain concentrations propoxyphene and norpropoxyphene delay cardiac conduction and diminish myocardial contractility in animals. Review of reports of human propoxyphene overdose that include cardiac or ECG findings suggests that respiratory depression, apnea, anoxia, and acidosis are primarily responsible for the cardiac and ECG abnormalities observed. It is suggested that more attention be paid to the correction of acidosis in the management of propoxyphene overdose. Serial ECG tracings in subjects on large doses of propoxyphene in a heroin-detoxification program, and 24-hour Holter monitoring of the ECG in two volunteers given propoxyphene every four hours for one week, failed to reveal any significant ECG changes.

Propoxyphene is an opioid possessing a pharmacological and toxicological profile similar to the chemically related methadone. It is well absorbed orally in animals and man and rapidly metabolized by N-demethylation in the liver to norpropoxyphene, the major plasma metabolite in the dog and man.