its combinations for the Panel. On November 24, 1970, I appeared before this Subcommittee to discuss the relative merits of various mild analgesics in the relief of pain, and a portion of this testimony was devoted to a critique of propoxyphene (Darvon®). From 1969 to 1976, I served as a consultant for the Food and Drug Administration, primarily on matters related to analgesic drugs and the design and interpretation of controlled clinical trials for drug efficacy. While serving as a consultant for the FDA, I prepared a special critique of the efficacy of propoxyphene based on my review of the published literature and the New Drug Applications for various propoxyphene products. This critique, submitted to Henry E. Simmons, M.D., Director, Bureau of Drugs, plus recommendations for revision of the propoxyphene labeling served as the basis for the relabeling of propoxyphene products which occurred in 1972. In 1976, I assisted the FDA in revising the propoxyphene labeling to reflect increased medical awareness [Finkel *et al.*, 1976; McBay and Hudson, 1975] of the incidence of fatal overdose with propoxyphene alone and in combination with other central nervous system depressants. I subsequently served as a FDA consultant to their Controlled Substances Advisory Committee in the matter of the advisability of scheduling Darvon under the Controlled Substances Act. The Committee recommended placing propoxyphene products in Schedule IV. The Department on Health, Education, and Welfare concurred in this recommendation, and, in February 1977, the Drug Enforcement Administration issued an order to that effect. Since 1976, I have continued to follow the literature on propoxyphene, in part because I am Chairman, Advisory Panel on Analgesics, Sedatives and Anti-inflammatory Agents for the 1975–1980 revision of the United States *Pharmacopeia*.

In addition, for the purpose of this testimony, I have studied a letter dated November 21, 1978 from Dr. Sidney Wolfe of the Health Research Group to Joseph Califano, Secretary of the Department of Health, Education, and Welfare urging an immediate ban on the marketing of propoxyphene as an imminent hazard under the Food, Drug and Cosmetic Act, and a petition by the same group to the Attorney General of the United States and the Drug Enforcement Administration resquesting the transfer of propoxyphene from Schedule IV to Schedule II under the Controlled Substances Act. I have read those literature references cited in that petition with which I was not already familiar and have reviewed the response to the letter to Secretary Califano prepared by the Eli Lilly Company and submitted to the Food and Drug Administration on December 28, 1978. I have also reviewed those clinical trials relevant to the analgesic efficacy of propoxyphene products appearing in the archival literature since my review of this subject for the Food and Drug Administration dated May 18, 1971. The critique which follows represents my opinions derived from examination of the above cited data base, my general knowledge and experience as a clinical pharmacologist primarily concerned with the clinical evaluation of analgesic drugs and my experience as a clinician and consultant responsible for the use of analgesics in the management of patients with various acute and chronic painful states.

GENERAL PHARMACOLOGIC PROPERTIES OF PROPOXYPHENE

Propoxyhene or dextropoxyhene (Darvon®) is structurally related to the potent narcotic methadone and is itself a narcotic in all pharmacologic and toxicologic respects. It produces the full spectrum of pharmacologic effects in animals and man characteristic of the narcotics, and these effects are selectively reversed by the specific narcotic antagonist naloxone. Quantitatively, however, propoxyphene is substantially less potent on a milligram basis than narcotics such as morphine, hydromorphone (Dilaudid®) and methadone. In addition, high doses of propoxyphene have certain excitatory properties not noted with most other narcotics which, while they tend to discourage deliberate abuse of propoxyphene, make convulsions a common feature of propoxyphene overdose in addition to the usual narcotic overdose manifestations of respiratory depression and coma.

ANALGESIC EFFICACY

On reviewing reports of studies which have appeared in the interim, I find little necessity to modify my evaluation of the efficacy of dextropropoxyphene which appeared in 1966 [Beaver, 1966] and which I presented in my testimony before this Subcommittee on 24 November 1970.