

A Study of the Abuse Potential of
Dextropropoxyphene
with Control Recommendations

Drug Control Division
Bureau of Narcotics and
Dangerous Drugs
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Introduction

Dextropropoxyphene was first marketed by Eli Lilly and Co. in 1957 as an analgesic or pain relieving drug. It rapidly gained widespread clinical acceptance as a safe, effective and nonaddicting replacement for codeine and became one of the most commonly prescribed drugs in the United States. Over the years since its introduction, evidence has accumulated that dextropropoxyphene is neither as safe nor as nonaddicting as first believed. Dextropropoxyphene has been abused both orally and intravenously and is the cause of a growing number of deaths.

This paper presents evidence that dextropropoxyphene is a central nervous system acting narcotic analgesic drug of the same type as morphine and codeine and as such that it can produce euphoria and physical dependence of the morphine type. Quantitatively, its ability to produce euphoria and physical dependence is less than morphine's and possibly less than codeine's. Further, this paper presents evidence of the actual abuse of dextropropoxyphene by both oral and intravenous route and presents an assessment of the present day extent of that abuse in the United States.

I HISTORY OF CONTROL

Propoxyphene was synthesized by Pollard and Sullivan in 1953 and the patent rights assigned to Eli Lilly and Co. Lilly began to market dextropropoxyphene (as Darvon) in 1957. The question of controlling propoxyphene was raised prior to this marketing by the World Health Organization (WHO). On December 14, 1955, WHO placed propoxyphene in Group II of the 1931 Convention and stated that the regime applicable to the drugs in Group II should be applied to propoxyphene. The Bureau of Narcotics then took action to control propoxyphene under the Federal Narcotic Laws and published in the Federal Register of February 27, 1956, a notice of proposed finding. Eli Lilly and Co. entered a formal protest and requested a hearing. No decision was made at the hearing, and the Bureau of Narcotics recommended that the matter be referred back to WHO for reconsideration. Subsequently, the Committee on Drug Addiction and Narcotics of the National Research Council expressed the opinion that propoxyphene had addiction liability substantially less than codeine (March 29, 1957).

WHO reviewed the case on propoxyphene and, on October 30, 1957, decided that it should remain controlled under Group II of the 1931 Convention, but the Bureau of Narcotics took no

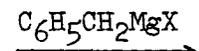
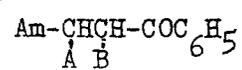
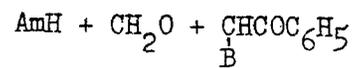
further action to control it under the Federal Narcotic Laws since the law at that time allowed control of a narcotic drug only if it had addiction forming and addiction sustaining liability similar to morphine. On February 5, 1959, WHO made a third decision on propoxyphene holding that "propoxyphene is no more addiction producing than codeine nor convertible into an addiction producing drug with morphine-like effects" and concluded that the drug is not subject to control under the 1931 Convention. However, in the interest of public health, WHO recommended that world governments place propoxyphene under a control regime similar to Group II.

The Manufacturing Act of 1960 allowed the Bureau of Narcotics to control a drug if required to do so by treaty. This act eliminated the "morphine-like" issue discussed above but by 1960 there was no treaty requirement for control as WHO had rescinded its order. On March 24, 1962, the Bureau of Narcotics published in the Federal Register its conclusion that propoxyphene would not be controlled under the Federal narcotic laws.

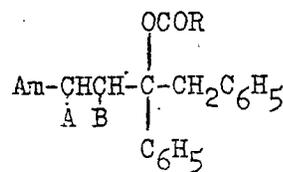
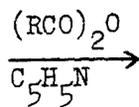
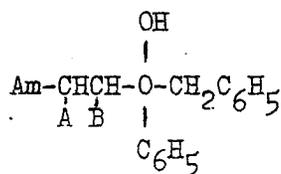
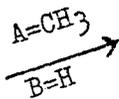
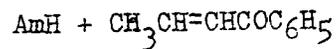
II CHEMISTRY

a) Synthesis

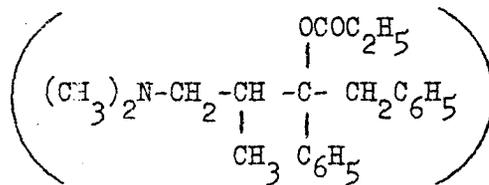
The synthesis of propoxyphene was reported by Pohland and Sullivan in 1953. A series of esters of 4-dialkylamino-1, 2-diphenyl-2-butanols were synthesized by the general procedures outlined below. The intermediate B-dialkylamino-propiofenones (I) were prepared by means of the Mannich reaction when the unbranched ethylene chain or the isomethadone-type branched chain was required. Addition of secondary amines to phenyl propenyl ketone gave the corresponding intermediates with the methadone-type branched chain. Treatment of these amino ketones with benzylmagnesium chloride gave predominantly one diastereoisomer, the alpha-carbinol, together with minor amounts of the beta-carbinol, which was separated by solubility differences. They were usually converted to the acylated derivatives (II) with acetic or propionic anhydride and pyridine. These acyl derivatives were quite resistant to hydrolysis. The racemic alpha-carbinol has been resolved by fractional crystallization of the (+)-camphorsulfonic acid salt and the optically active carbinol hydrochlorides acylated to give (+)- and (-)-propoxyphene.



I



II



Propoxyphene

Subsequently Sullivan, Beck and Pohland (1963) reported the absolute configuration of dextropropoxyphene to be (2S:3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane.

b) Chemical Relationships

Propoxyphene (4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane) is structurally related to methadone and isomethadone. The structure of this class of analgesics, as conventionally written, is quite different from that of morphine, but molecular models reveal its essentially morphine-like structural feature. Of the three compounds, the pharmacological activity of methadone is most similar to morphine for which it can substitute completely. Despite its chemical similarities, propoxyphene cannot be converted into methadone or isomethadone.

The propoxyphene molecule has two centers of asymmetry and exists as four stereoisomers. Of these the alpha-d-isomer, dextropropoxyphene, is analgesic and the alpha-l-isomer, levopropoxyphene; has significant antitussive activity. The beta-distereoisomers are substantially inactive, and cannot be readily converted into the alpha-distereoisomers.

c)

Eli Lilly and Co., as patent holders, have been the sole manufacturer of dextropropoxyphene which they market as Darvon^R. However, the patent on the hydrochloride salt of dextropropoxyphene expired in December 1972. As of December 1975, 27 companies have had NDA's approved allowing them to market dextropropoxyphene HCl. In anticipation of this, Lilly has submitted and had approved an NDA on dextropropoxyphene napsylate (Darvon-N) on which they expect to have patent protection. They will continue to market dextropropoxyphene hydrochloride as Darvon^R.

At present, Lilly has approved NDA's for 20 preparations containing dextropropoxyphene and 4 preparations containing levopropoxyphene not all of which are being marketed.

The FDA presently lists 27 additional companies which hold NDA's on a total of 56 propoxyphene formulations. Many of these NDA's are for formulations which duplicate one or more of Lilly's formulations.

It is understood that dextropropoxyphene is marketed in an injectable formulation outside the United States.

In the original formulations of Darvon with ASA and Darvon compound, all the ingredients were mixed in a single powder.

It soon became apparent that this method of formulation permitted the rapid chemical breakdown of active ingredients. Lilly then reformulated these preparations as capsules which contained a pellet of dextropropoxyphene while the other ingredients were loose in the capsule. This pellet was dissolved by some drug abusers and injected intravenously. In order to counter this method of abuse, Lilly, in 1971, again changed the formulation of these products by eliminating the pellet, dispersing the propoxyphene throughout the mixture and adding other inert ingredients. It should be noted that at least one of the other companies now marketing dextropropoxyphene utilizes the pellet in their formulation with aspirin. In relation to their new salt, Lilly states in their advertisement, "Propoxyphene napsylate is a water insoluble salt of propoxyphene". With this in mind, the Special Testing and Research Laboratory of BNDD was requested to determine the ease of isolation of the active ingredients, in a form suitable for injection of the various dosage forms of Darvon. The results of this study are detailed in a memorandum, Exhibit IV from Mr. Stanley P. Sobol, Chief Chemist, dated November 26, 1971. His conclusions are quoted below.

Darvon:

"For all practical purposes, there is little or no difference between the hydrochloride and napsylate salts of

propoxyphene in regard to their abuse potential. Although the napsylate is not very soluble in cold water, its solubility in hot water approximates that of the hydrochloride and it is common practice for the abuser to heat preparations to solubilize the drug."

"Therefore, either salt of propoxyphene is easily isolated from those dosage forms containing no other active ingredients by dissolving the powder in warm water and filtering. No breakdown of propoxyphene was detected when subjected to heating under the conditions described. The presence of methylcellulose in the napsylate preparations causes no difficulty in the dissolution of the powder or viscosity of the filtrate. The resulting solution is clear, free-flowing, and could be used for injection."

"For those preparations where the propoxyphene salt is compounded with ASA, APC, or phenaglycodol, the 'ease of isolation' is a subjective judgment. In all instances, preliminary washing with ether will remove most of the other material and the propoxyphene salt can be recovered using the same procedure as outlined above; however, recovery of the propoxyphene salt is rather low in some cases".

In reviewing the original May 1973 issue of this document, representatives of Eli Lilly & Co. objected to the results of the above quoted document and reiterated their opinion that propoxyphene napsylate is essentially insoluble in water (either hot or cold) and thus not abusable by the

intravenous route as a water solution. In order to clarify this discrepancy, additional studies were performed in the DEA Special Testing and Research Laboratories. The results of these studies are presented in Exhibit V, a memorandum from Mr. Stanley P. Sobol, Laboratory Director, dated January 7, 1976, and titled "Propoxyphene Solubility". In the performance of this study, strict conditions were imposed in order to duplicate as far as possible the usual conditions under which heroin users prepare their material for injection, which method is also used by individuals preparing propoxyphene for injection. One to four tablets of Darvon-N 100 mg. were dissolved in 5 or 10 ml. of water (one or two spoonfuls) with mild heating. The resultant solution was filtered through cotton and analyzed for propoxyphene concentration. One hundred milligrams of propoxyphene napsylate standard was treated in a similar manner. The results of this study showed that the maximum quantity of propoxyphene napsylate that could be obtained in solution would be in the order of 9 mg. using 5 ml. of water and 24 mg. using 10 ml. of water. These results confirm Lilly's contention that propoxyphene napsylate is essentially not abusable by the intravenous route as a water based solution.

It is evident that the present formulation of dextropropoxyphene hydrochloride can be dissolved in a spoon, filtered through cotton and injected as in the usual procedure for heroin. The formulations with ASA, APC, or phenaglycodol require more effort to extract the dextropropoxyphene than the abuser is liable to take, but there is really no reason for removing the other drugs. They can be expected to neither interfere with nor enhance the effect of the dextropropoxyphene nor are they as toxic as the dextropropoxyphene. Injection of these "new" formulations can be expected to have neither more nor less harmful effect on the cardio-vascular system than that caused by injection of the crushed pellet. The formulations of the 27 new manufacturers of dextropropoxyphene can be expected to be equally easy to dissolve and most of them have only dextropropoxyphene as an active component.

d) BNDD Laboratory Analysis of Dextropropoxyphene HCl

During the period from July 1, 1970 through February 24, 1973.

BNDD laboratories reported the analysis of 424 exhibits of dextropropoxyphene. Figure No. 1 presents graphically the number of exhibits analyzed plotted by the date the exhibit was received. Noting that there is a delay of up to three months between the receipt of an exhibit and its reporting as a BNDD analysis, thus making the figures for the last three months incomplete, there is still an indication of an increase in the number of exhibits received during 1972 as compared with those received during 1971.

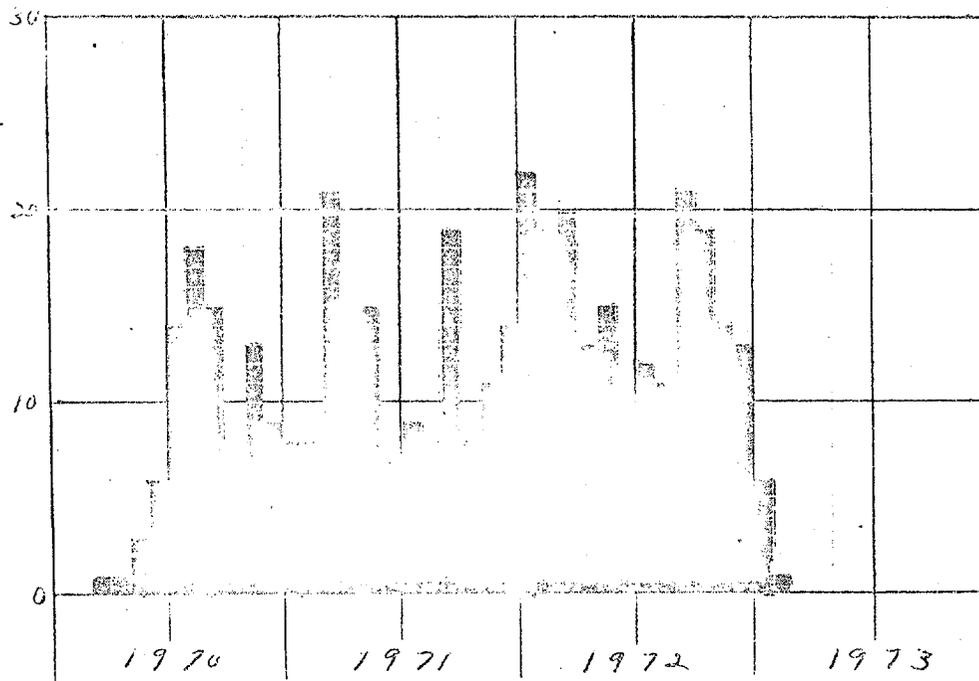


Figure Number 1: BNDD Laboratory analysis of dextropropoxyphene by month in which the sample was submitted.

III ABSORPTION, DISTRIBUTION AND METABOLISM

a) Absorption and Distribution

Dextropropoxyphene has been used as the hydrochloride salt and is now also available as the napsylate salt. Both salts are orally effective but the hydrochloride is more rapidly absorbed (Fig. 2).

FIGURE 2

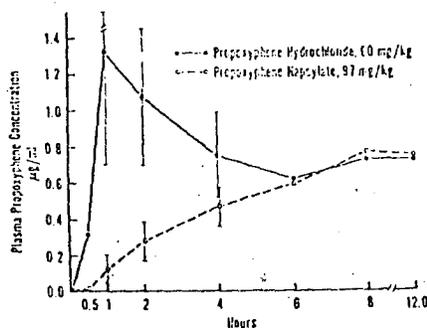


FIG. 1. Mean plasma propoxyphene concentrations for groups of 4 dogs. SE for the 6-, 8-, and 12-hr samples were $\pm 0.2 \mu\text{g/ml}$; they were omitted for clarity.

From Emmerson, Gibson and Anderson, *Toxicol. Applied Pharmacol.*, 19: 445, 1971.

The relative absorption of these two salts as shown by both peak plasma concentration and total area under the curves clearly indicates that the primary site of absorption is intestinal rather than gastric. From the plasma concentration curve it is apparent that a greater proportions of the hydrochloride salt is absorbed during the first 12 hours after dosing. It would be useful to carry this blood level

study on until plasma clearance of propoxyphene is essentially complete in order to explore the possibility that the napsylate salt acts as a "slow release formulation" and is ultimately as completely absorbed as the hydrochloride. If this were true, an individual taking an excessive amount of the napsylate salt for its immediate effect would be exposed to toxic doses for a long period of time.

In the study of Emmerson et al., the napsylate salt, at equivalent doses, was found to have less acute toxicity than the hydrochloride (Fig. 3).

FIGURE 3

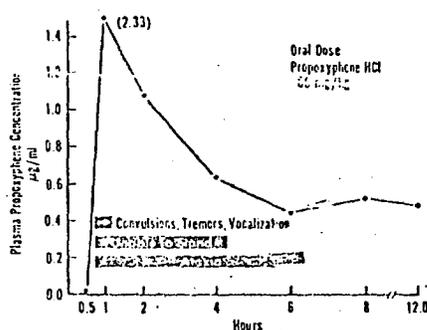


FIG. 2. Plasma propoxyphene concentrations and toxicologic signs in a dog given propoxyphene HCl.

From Emmerson, et al. (1971).

This effect is clearly a function of their relative rate of absorption resulting in a dose of the napsylate salt never producing the high plasma concentrations produced by the hydrochloride salt. In addition to making the napsylate salt less toxic, its relatively slower absorption would be expected to delay the onset of analgesia and decrease the maximum intensity of analgesia. Thus one

would expect that relatively larger doses of the napsylate, on a molecular basis, would be taken for a similar analgesic effect and consequently nullify its apparent lesser toxicity.

The well-controlled study of human plasma concentrations of dextropropoxyphene following oral administration by Nash and co-workers (1971) shows a significant individual variation of absorption (Fig. 4).

FIGURE 4

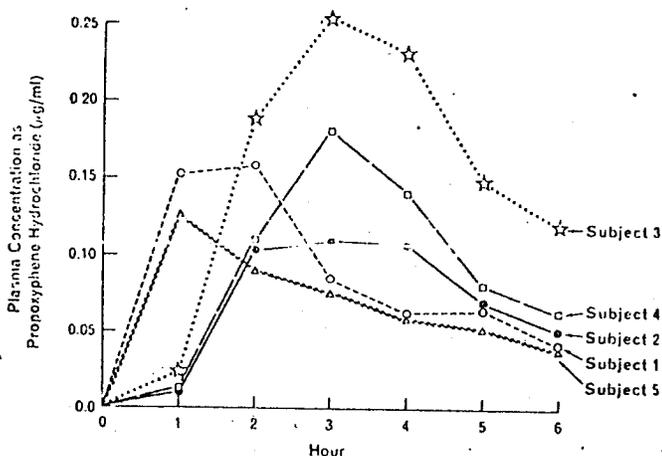


FIG. 5. Plasma concentrations in individual human subjects after administration of 200 mg of propoxyphene napsylate in the capsule formulation.

From Nash, J.F., Scholz, N.E. and Maxwell, S.B.,
Toxicol. Applied Pharmacol., 19: 537, 1971.

With this magnitude of individual variation it can be expected that subject two would have to take at least twice the dose of propoxyphene napsylate to reach the

same level of analgesia as subject three. Similarly, subject three with his more complete absorption would be more likely to suffer the effects of accidental or intentional overdose.

b) Metabolism

Metabolic studies of dextropropoxyphene have been performed in the rat (in vitro and in vivo) and in man (in vivo). Lee, Scott and Pohland (1957 and 1959) incubated $N^{14}CH_3$ labeled propoxyphene with slices of rat liver, kidney, brain and whole blood. The liver slices yielded 12.3% of the radioactivity as $^{14}CO_2$ after 30 minutes incubation, indicative of metabolism by N-demethylation. The kidney slices also showed evidence of N-demethylation but only at 0.5-2.5% of that found in the liver. Intravenous injection, in rats, of $N^{14}CH_3$ labeled propoxyphene yielded 38% of the radioactivity, as $^{14}CO_2$, in expired air, 15% in the urine and 35% in the faeces.

In three human volunteers, receiving 100 mg orally every 4 hours for 16 hours, only 3%, 10%, and 3% of the drug was recovered in the 24-hour urine. The N-demethylated metabolite, des-N-methylpropoxyphene, was recovered in the urine of these subjects.

Amundson, Johnson and Manthey (1965) administered 65 mg of dextropropoxyphene orally to eight male subjects and determined, qualitatively and quantitatively, the metabolites in urine samples collected at two-hour intervals for 12 hours and at 12-hour intervals for 48 hours. Twenty-five percent of the dose was excreted in the urine, unmetabolized drug mainly in the first six hours and metabolite (des-N-methylpropoxyphene) mainly after six hours. Most of the dose was excreted as the N-demethylated metabolite.

IV PHARMACOLOGY

a) Animal

1) Analgesia in Animals

The majority of presently known analgesics may be classified in one of two distinctly different classes, the periferally acting antipyretic/anti-inflammatory group (typified by aspirin) and the centrally acting narcotic group (typified by morphine). Classification of analgesics is based on their effectiveness in man against only certain types of pain, their relative activity in certain animal models of pain and their site of action being either central or periferal.

The relative analgesic activities of dextropropoxyphene and aspirin in various pharmacological models of pain in animals are presented in Table 1. The pattern of activity of dextropropoxyphene is typical of a centrally acting analgesic of the morphine type. Those procedures which produce inflammation or local irritation exhibit the best analgesic response to aspirin, while almost all the responses to a painful stimulus are altered by dextropropoxyphene. The tailjerk-rat and hot plate-mouse tests present a painful stimulus which is insufficient to cause physical damage and the positive response is an escape from the stimulus within a certain minimal time. Only a centrally acting drug will be positive

in this test. In contrast, the ultra-violet light induced erythema is a local response of the skin, essentially a mild burn, and its reduction is characteristic of an anti-inflammatory agent. The most distinguishing test is that of paw pressure in the rat, dextropropoxyphene raises the pain threshold of both normal and inflamed paw while aspirin raises the pain threshold only in the inflamed paw. The antipyretic activity of aspirin is a central effect on the temperature control centers of the hypothalamus, but the narcotic analgesics do not possess any antipyretic effect.

Table 1

Test Procedure	Response* to	
	Propoxyphene Hydrochloride	Aspirin
Tail jerk--rat†	2+	0
Hot plate--mouse‡	2+	0
Writhing--mouse§	3+	2+
Paw pressure--rat		
Normal paw	2+	0
Inflamed paw	3+	2+
Antitussive activity	1+	0
Inhibition of ultra-violet induced erythema	0	3+
Antipyretic	0	3+
Respiration	Depression	Stimulation

*0 signifies no effect; 1+, slight effect; 2+, moderate effect; and 3+, marked effect.

†Rat's tail is held at constant distance from heated wire until radiant heat causes rat to "jerk" tail away; response is timed.

‡Mouse is placed on "hot plate" (constant temperature surface) until mouse makes a stereotyped gesture of discomfort; response is timed.

§Mouse is injected intraperitoneally with chemicals which produce typical writhing and stretching response which is blocked by analgesic agents.

From F.G. Kiplinger & R. Nickander, Pharmacologic Basis for Use of Propoxyphene, JAMA, 216:289, 1971

The central site of activity of dextropropoxyphene was clearly established by Lim et al. (1964), in studies on the dog. Injection of small doses of bradykinin into the splenic artery of the dog produced a stereotyped response to this painful stimulus. Experimental animals were prepared so the neuronal tract to the spleen was intact but the circulation was isolated and perfused by a second animal. In this preparation salicylates block the response to bradykinin when injected locally into the spleen. In contrast, morphine decreased the pain response when injected systemically and could enter the brain but not when injected locally into the spleen. Dextropropoxyphene (like morphine) blocked the evoked response to bradykinin only when given by a route which allowed it access to the brain.

2) Self-administration of dextropropoxyphene by rhesus monkeys

Balster, Schuster and Wilson (1971) reported a study in which rhesus monkeys self-administered dextropropoxyphene intravenously to the point of incapacitation brought on by drug induced toxic convulsions. These monkeys had been previously stabilized on self-administered doses of cocaine and morphine, sequentially not simultaneously. This study indicated that drug-experienced monkeys would self-administer dextropropoxyphene to the point of overdose toxicity.

Tally and Rosenblum (1972) were able to show that rhesus monkeys would self-administer dextropropoxyphene intravenously without prior experience with any other drugs. These animals too continued self-dosing until toxic convulsions occurred. When the animals recovered from the incapacitating effects of the convulsions, they resumed self-administration of dextropropoxyphene. A dose of 0.5 mg/kg/lever press was sufficient to initiate self-dosing by the monkeys.

b) Human

1) Analgesic Effects in Man

Dextropropoxyphene is indicated for "the relief of mild to moderate pain" (Exhibit I). The FDA committee on drug efficacy has reviewed the clinical studies of dextropropoxyphene and has concluded that the drug is effective at a dose of 65 mg.

2) Human Abuse Potential

Fraser and Isbell (1960) have reported a series of studies of the addictive liability of dextropropoxyphene in human subjects at the Lexington facilities. Administered orally to nine post-addicts (morphine-heroin), dextropropoxyphene at single doses of 355 to 650 mg produced subjective effects which the patients liked and related to the effects of marihuana, heroin, morphine

and cocaine. With doses of 650 mg, nausea, vomiting, sedation and depressed respiration were consistently present. Single subcutaneous doses of 120 or 250 mg produced minimal subjective feelings of morphine effects in three of six patients.

The ability of dextropropoxyphene to substitute for morphine in physically dependent subjects was examined in two studies. In the first study morphine was abruptly withdrawn from eight subjects who had been stabilized on 250 to 280 mg/day. At 0, 6, 14 and 20 hours after the last dose of morphine, 200 mg of dextropropoxyphene was given orally. This dosage regimen significantly reduced the intensity of the abstinence syndrome. In the second study, a double-blind study with addicted patients, dextropropoxyphene orally was substituted for morphine for 14 days. The maximum tolerated dose of dextropropoxyphene was found to partially suppress the morphine abstinence syndrome. The ability of dextropropoxyphene to produce physical dependence was studied in 5 post-addiction patients who received dextropropoxyphene orally (600-825 mg/day) for 53 days. Initially, subject effects and behavior partially resembling those seen after morphine were observed but these rapidly subsided. Following 10 mg of nalorphine intravenously 2 of the 5 subjects showed abstinence signs of a slight degree. After abrupt termination of dextropropoxyphene minimal abstinence symptoms consisting of weakness, aching, yawning,

lacrimation, diarrhea and perspiration were observed.

The intravenous abuse potential of dextropropoxyphene was accessed by Fraser (1964) who compared the effects of intravenous morphine, dextropropoxyphene and I-O-I in each of 12 subjects. The subjects were all post-addiction patients at Lexington. The drugs were administered by slow intravenous injection (2 minutes) in a randomized crossover, double-blind experiment. The author stated that "Such a slow rate of intravenous injection greatly reduces the intensity of drug effects; in fact, it is difficult to identify morphine by this procedure since no subjective 'tingling' or objective flushing is observed."

The results of this study are summarized in Table 2. In three of the five parameters evaluated, d-propoxyphene did not differ significantly from morphine.

Table 2

TABLE 1

Average effects of morphine (20 mg), *d*-propoxyphene (180 mg) and I-O-1 (300 mg) when given in single doses intravenously (total response scores of patients \pm SEM)

Drug	Parameter being evaluated				
	"Feel drug"	Identified as "dope"	Opiate symptom score	"Liking" score	Decrease in pupil diameter
Morphine	4.67 \pm 0.61	4.58 \pm 0.65	19.17 \pm 4.45	7.50 \pm 1.35	10.04 \pm 1.56
<i>d</i> -Propoxyphene	3.42 \pm 0.55	3.17 \pm 0.67	13.42 \pm 2.93 ^b	6.50 \pm 1.29	7.40 \pm 1.21 ^a
I-O-1	2.50 \pm 0.62 ^a	1.92 \pm 0.74 ^b	7.25 \pm 2.56 ^b	4.25 \pm 1.25 ^a	4.54 \pm 1.19 ^b

^a Indicates that the value is significantly different from morphine ($P < 0.05$).
^b Indicates P is < 0.01 by the paired t -test. Note that all parameters are significantly different from morphine in the case of I-O-1, but only two para-

eters are significantly different in the case of *d*-propoxyphene. When I-O-1 and *d*-propoxyphene were compared, significant differences were observed for the parameters, the opiate symptom score, and decrease in pupillary diameter ($P < 0.01$).

From: Fraser, H.F., U.N. Bulletin on Narcotics, Vol. 16 (1) 37; 1964

V TOXICOLOGY

a) Animal

Harpel and Mann (1965) reported that nalorphine pretreatment increased the survival rate of mice injected intraperitoneally with a lethal dose of propoxyphene. Mann (1967) subsequently expanded these studies and demonstrated a significant antidotal effect of nalorphine. The intraperitoneal LD₅₀ of propoxyphene was determined to be 118 (106-131) mg/kg and an LD_{99.5} dose (200 mg/kg) was selected as the lethal dose to be used in these antidotal studies. This dose was found to be actually lethal to 49 of 50 mice (98%). A second group of 50 mice, pretreated with nalorphine HCl (0.1 mg/mouse) five minutes prior to dosing with propoxyphene (200 mg/kg), demonstrated both a significant increase in mean survival time (46%) and a significantly larger number of survivals (6).

The nalorphine antagonism of the convulsive and lethal effects of dextropropoxyphene in rats was studied by Chapman and Walaszek.(1962). The intraperitoneal injection of 40 mg/kg dextropropoxyphene consistently produced a syndrome consisting of, sequentially, a symptomless period (3-5 minutes), a period of catatonic-like depression

(5-10 minutes) and a period of clinic convulsions. The Straub tail was frequently seen during this last period. Doses greater than 80 mg/kg produced convulsions of brief duration ending in death by respiratory arrest. The intraperitoneal LD₅₀ of dextropropoxyphene was found to be 68 mg/kg. Not only was pretreatment with nalorphine effective but post-treatment also caused a significant reduction of the toxic effects of dextropropoxyphene. As shown in Table 3, both mortality and mean convulsant periods were reduced in dose related manner.

Table 3

THE EFFECT OF NALORPHINE ON ESTABLISHED CONVULSIONS INDUCED BY DEXTROPROPOXYPHENE

Dextro-propoxy-phene (mg/kg)	Nalorphine ^a (mg/kg)	Number of rats	Mortality (%)	Mean convulsant period ^b (minutes)
65	0	8	50	49.6 ± 5.8
65	0.1	8	12.5	25.8 ± 3.3
65	0.5	8	12.5	19.8 ± 1.6
65	20	8	0	5.1 ± 1.6

^a Nalorphine was administered at the time of the initial convulsion.

^b Convulsant period is a measure of the duration in minutes of the dextropropoxyphene-induced convulsions.

From Chapman, J.E., and Walaszek, E.J., Antagonism of Some Toxic Effects of Dextropropoxyphene by Nalorphine; Toxicol. & Applied Pharmacol:4, 752, 1962.

The authors also investigated the site of the dextropropoxyphene induced convulsions in rats having the spinal cord sectioned at the level of the 6th cervical vertebra. Dextropropoxyphene

produced convulsant activity in the head, neck and anterior limbs but not in the posterior limbs. The lethal effect was unchanged.

Dubas and Parker (1971) reported that pretreatment of mice with the morphine antagonist naloxone (10 mg/kg) significantly decreased the toxicity of dextropropoxyphene. In distinct contrast, the toxicity of levopropoxyphene (which has no analgesic activity) was not effected by the same dose of naloxone.

The most elegant study of the effect of morphine antagonists on dextropropoxyphene toxicity was performed by Fiat, Picchioni and Chin (1966). They infused dextropropoxyphene intravenously at a constant rate into mice and rats and determined the mean convulsant threshold and mean mortality threshold doses. Pretreatment with the morphine antagonists levorphan, nalorphine or naloxone increased the mean convulsive threshold dose of propoxyphene by 60%, 41% and 23% in mice and 50%, 57% and 60% in rats respectively. The mean mortality threshold dose in mice was increased 60%, 50% and 59% and in rats it was increased 114%, 127% and 132% by the respective antagonists. In no case did these antagonists eliminate convulsions in any treated

animal. In distinct contrast, pretreatment with pentobarbital completely protected 50% of the mice and 70% of the rats from convulsions during propoxyphene infusion but had no effect on the mean mortality threshold dose in either species.

It can be concluded that the toxic effects of dextropropoxyphene are due to its interaction with morphine-type receptors in the central nervous system.

b) Human

In the majority of reported cases of dextropropoxyphene poisoning, the dose ingested is unknown. However, in a sufficient number of cases the dose is reported so that some estimate of a lethal dose in man may be made. Table 4 summarizes the data from 8 cases of acute dextropropoxyphene poisoning taken from the medical literature. In all of these cases the total dose, age, sex, treatment and outcome are reported while in two cases the dose in mg/kg is reported. In each case the dose taken was sufficient to cause respiratory arrest which required mechanical support. Thus, one is justified in assuming that the doses in this series would have been lethal without medical intervention. All the patients received symptomatic treatment and in addition; six patients received nalorphine. Three patients died of cerebral damage secondary to anoxia. Two of these latter patients were treated

with nalorphine but failed to respond indicating that cerebral anoxia had already produced irreversable damage. This data indicates that timely administration of the morphine antagonist nalorphine in sufficient dose reverses the respiratory depression/arrest of acute dextropropoxyphene poisoning in man.

Table 4

Acute Dextropropoxyphene Poisoning in Man

<u>Age</u> <u>Sex</u>	<u>(yr)</u>	<u>Dose</u>	<u>Treatment</u>	<u>Disposition</u>	<u>Autopsy</u>
2M		4x65mg	Symptomatic	Survived	-
	Hyatt (1962)				
3 $\frac{1}{4}$ F		5x32mg 10.7mg/kg	Symptomatic Nalorphine	Survived	-
	Billig (1968)				
4M		9x65mg	Symptomatic Nalorphine	Survived	-
	Swarts (1964)				
15F		40x32mg	Symptomatic Nalorphine	Died	Cerebral Edema
	McCarthy & Keenan (1966)				
15F		30x32mg	Symptomatic Nalorphine	Survived	-
	Cawood & Thirkettle (1966)				
17F		28x65mg 32mg/kg	Symptomatic Nalorphine	Died +2 months	Anoxic Cerebral Damage
	Gary et. al. (1968)				
18F		26x32mg	Symptomatic Nalorphine	Survived	-
	Qureshi (1964)				
65F		35x65mg	Symptomatic	Died	Cerebral Damage
	Kerliner (1967)		Nalorphine		

VI CLINICAL USE

Eli Lilly & Co. distribute dextropropoxyphene as Darvon and Darvon-N (the hydrochloride and napsylate salts respectively) in the United States and, by virtue of their patent holdings, have been the sole source of this drug. The manufacturer recommends dextropropoxyphene "for the relief of mild to moderate pain" and as "useful for patients who may be sensitive to aspirin" (Exhibits I and II). This statement generally agrees with the human pharmacology which shows dextropropoxyphene to have 1/3 to 1/2 the effectiveness of codeine and to equal the effectiveness of the usual dose of aspirin in mild to moderate pain. However, dextropropoxyphene completely lacks the anti-inflammatory and anti-pyretic effects of aspirin.

In relation to the clinical use of dextropropoxyphene, Beaver (1970) states "The 65 mg dose is no more effective and possibly less effective than the usually used doses of aspirin. Although many physicians are currently prescribing 100 to 130 mg doses, the labeling specifies a usual dose of 65 mg three to four times a day." Similarly, the Journal of the D.C. Dental Society (1971) in discussing propoxyphene hydrochloride (Darvon) concludes "A 65 mg

dose of propoxyphene has mild analgesic effect and can be tried in patients in whom the usual doses of aspirin or acetaminophene are not effective or not tolerated."

Currently dextropropoxyphene is being used clinically, 1) in place of codeine in the belief that it is equally effective and less toxic or 2) in place of aspirin in the belief that it is more effective with no increased toxicity. In contrast, the human pharmacologic and toxicologic evidence clearly indicate that this rationale for clinical use is incorrect. Dextropropoxyphene is indicated only in cases of mild to moderate pain where the patient is unable to tolerate aspirin.

VII ABUSE

a) Oral

- 1) The summary of Eleson and Dominic (1963) is quoted in full.

Summary

"A case of dextropropoxyphene hydrochloride addiction has been reported. This addiction was characterized by extreme psychic craving, euphoria and tolerance to dextropropoxyphene hydrochloride. The patient stated that he had taken well over 1 gm a day of dextropropoxyphene hydrochloride, although this history was not conclusively verified. In any event, it was verified that in the hospital the patient was able to tolerate very well 780 mg of dextropropoxyphene hydrochloride. Within 24 to 48 hours (of admission), the patient showed definite withdrawal signs, including chills, profuse perspiration, cramps, abdominal pain, headaches, nervousness and diarrhea. It is suggested that in an occasional patient, abuse of dextropropoxyphene hydrochloride clearly can occur."

- 2) The Summary of Wolf et al. (1969) is quoted in full.

"A 31-year-old woman with long-standing psychiatric difficulty was introduced to propoxyphene (Darvon) by prescription after gynecologic surgery. She gradually developed a primary addiction and took an oral dose that at

times reached 2300 mg daily. She was hospitalized for drug withdrawal and initially maintained on 1300 mg propoxyphene daily. Laboratory evaluation showed no evidence of chronic liver, kidney or hematological toxicity. Placebos were then substituted for the propoxyphene and definite abstinence symptoms and signs occurred. These consisted of anoxemia, rhinitis and fatigue, followed by irritability and insomnia. Vomiting developed at the end of 48 hr. of abstinence. Propoxyphene was restarted, and within 24 hr. the patient was asymptomatic. We conclude that tolerance and physical dependence to propoxyphene can occur."

3) Mattson et. al. (1969) are quoted as follows.

"We have recently seen four patients who were chronically dependent on propoxyphene. The drug not only gave some pain relief, but when taken in increasingly larger doses, produced frank euphoria. The quantity of propoxyphene taken was increased gradually as some tolerance developed until the patients were taking 1000-1500 mg in a 24-hour period. Not only did the patients continue using the drug for its psychic effects, but three of them were unable to stop because discontinuation produced withdrawal symptoms characterized by perspiration, tremulousness and nausea

which were promptly relieved when more propoxyphene was taken. One patient developed a severe delirium lasting four days after discontinuation of the drug."

4) Salgnero et. al. (1969) have reported the case of a 20-year-old male with a "predominant psychic dependence on propoxyphene. Under the effects of propoxyphene the patient felt like a super hero and would approach situations with confidence and some aggressiveness. Propoxyphene made him relaxed, caused relief of tension and a mild euphoria." The patient reported a three-year history of continuous intake of the drug and an average daily consumption of 65 mg every two to four hours. At admission, he was reported to be taking up to 1500 mg of dextropropoxyphene per day. Withdrawal of the drug resulted in patient complaints of general malaise, chills and increased bowel movements. Propoxyphene, 780 mg a day, was then given for 20 days and a series of double-blind nalorphine tests were performed on the 15th, 16th and 17th day. No evidence of a precipitated withdrawal syndrome was obtained and the patient was abruptly withdrawn with minimal discomfort during the first week of withdrawal. Subsequently, the patient was found in his bed deeply intoxicated with signs resembling

those produced by narcotics, including nodding, drowsiness and miosis. A 48-hour urine collection yielded 76.4mg of propoxyphene and no evidence of other narcotics by chromatographic analysis.

5) Kane and Norton (1970) have reported the case of a 57-year-old white married man who had admitted himself "because of his concern about dependence upon a mixture of propoxyphene hydrochloride 65mg, aspirin 227mg, phenacetin, 162mg and caffeine, 32mg (Darvon Compound)."

The patient first took the propoxyphene mixture five years prior to admission during a depressed state, and it "immediately made him feel better, brighter and more cheerful, more able to interest and to relate to people and much less depressed."

At admission the patient was taking 16 to 20 tablets daily, and reported mild euphoria as an accompaniment to his drug use while feeling uncomfortable when he tried to stop. The patient exhibited moderate signs of chronic salicylate toxicity at admission. During a five-day withdrawal period, the patient suffered weakness, impaired sleep and fairly severe diarrhea.

6) Addiction to a Massive Dosage of Darvon

Fier (1973) reported the case of an individual taking 3.3 grams of propoxyphene (Darvon) daily. Of particular interest in this case is the description of the method by which the patient was able to obtain his supply of drug, which is quoted in full below. It should be noted that placing propoxyphene in Schedule IV would make this particular slight of hand impossible.

"At this point, his way of obtaining such large quantities of Darvon is worth mentioning. A physician had given him a prescription for 50 capsules of Darvon. By consulting two or three other physicians, he obtained additional prescriptions for Darvon. He became friendly with the pharmacist whose store adjoined that of his father's shop. The two young men would often chat, share coffee breaks, and eventually became friends.

While having a prescription for Darvon filled one day, he casually asked, 'How much would 100 cost me?' The pharmacist indicated that the price for 100 capsules would be better than for the prescribed 50. He gratefully told his friend to fill the prescription for 100 capsules. He had his three remaining prescriptions filled at different pharmacies, and was generally able to induce the pharmacists to sell him 100 capsules instead of the prescribed 50. He would then go to a pharmacist at some distance from the ones that had already filled the prescriptions. He would tell the pharmacist that he was away from home, needed Darvon for pain and that his home pharmacy held a bona fide prescription for the drug. The obliging pharmacist would then call the drug store that he had identified for him and the verification would follow. Indeed, the original pharmacist indicated that he had a valid prescription for 100 capsules of Darvon.

new pharmacist then sold him another 100 capsules of Darvon. When he reappeared at this new pharmacy two months later, his prescription would be refilled from the label on the bottle. This would be repeated at carefully spaced intervals to avoid suspicion. With three or four 'base' prescriptions, and about 27-30 'cooperating' drug stores, he was able to obtain this supply of approximately 1500 capsules monthly. The cost of the habit ranged from \$150 to \$200 per month. Since he returned to each drug store only once every 50-60 days, he did not arouse suspicion."

7) Naloxone Challenge in Propoxyphene Dependence

In 1974 Daftery reported two cases in which naloxone was administered to two individuals who had been ingesting excessive amounts of Darvon Compound-65.* One subject claimed to have been taking orally 40-60 capsules of Darvon Compound-65 for approximately two years and the second stated that he had consumed approximately 20 capsules daily for 7 years. The patients were allowed up to 10 capsules of the drug at four hour intervals for a week under medical supervision. The lack of adverse reactions to this near lethal dose was demonstrative of tolerance to dextropropoxyphene.

The patients were then challenged with intra-muscular naloxone (0.8 mg.) or an equal volume of saline in a double-blind manner. "Naloxone administration was associated with uncontrollable yawning, profuse diaphoresis, lacrimation, rhinorrhea, myalgia, severe abdominal cramps with nausea and involuntary evacuation of intestinal contents, mydriasis, hypertension and elevations of systolic and diastolic blood pressures in excess of 20 mm Hg above basal reading. Onset of symptoms was prompt, occurring within 15 minutes and persisting for approximately three hours". "Placebo administration did not elicit withdrawal."

*Dextropropoxyphene 65 mg., aspirin 227 mg., phenacetin 162 and caffeine 324 mg.). 37c

8) Addiction to Propoxyphene (Darvon) A Second Look
Maletzky (1974) reported seven cases of primary dependence (basically physical) to propoxyphene characterized by tolerance to an abnormally high daily dose and the appearance of a withdrawal syndrome upon abrupt withdrawal of the drug. In all cases the patients had no history of drug abuse or psychic abnormalities that might be considered predisposing to drug abuse. In each case, propoxyphene was first presented as legitimate therapy for pain. The patients continue to take the drug in increasing doses until circumstances brought their condition to the attention of physicians knowledgeable of drug dependence. Data on these cases is summarized below.

Source of Drug	Maximum Dose taken mg/day	Duration of Self Admin.	Maximum Dose given During Hosp. mg/day	Sex/Age
Prescription	1560	2 years	1560	M 20
Prescription & "Pusher"	2275	not given	2080	M 45
Prescription	not given	3 years	1560	F 35
Prescription	1625	1 year?	1625	M 19
Prescription	2000	4 years	not stated	M 52
Prescription & "Pusher"	1950	6 months	not stated	F 23
Prescription	not given	several years	Methadone 10 mg/6 hrs.	M 32

b) Intravenous Abuse

1) Collins and Mathis (1967) have reported two cases (a married couple) of intravenous abuse of dextropropoxyphene. The husband began taking barbiturates and amphetamines in his middle teens and graduated to narcotics which led to his commitment to the Fort Worth Institution at 22 years of age. Upon his release, he found his wife "addicted" to Demerol.

"They live in an area in which narcotics are not readily available. Other addicts informed them that a capsule, Darvon compound, could be obtained from any physician for headache, backache and so forth. The small tablet of propoxyphene hydrochloride contained in each capsule of the compound can be removed and the powder discarded. It does not dissolve readily, but it may be crushed in a small amount of water, sucked into a syringe through a cotton filter and injected intravenously. At the time of consultation, the husband required 12 of these tablets at one dose. He, an experienced addict, described the effect as much the same as intravenous codeine, but lying somewhere between morphine and codeine. It is no means as satisfactory as narcotics, but gives a good "jolt" and temporarily prevents withdrawal symptoms. There are

unpleasant side effects of mild nausea, an aching in the joints and muscles and a sensation of chilling and fatigue five to eight hours after the "fix."

2) Batz (1969) has reported a case of pulmonary arteriole foreign body granulomate resulting from the intravenous injection of an oral formulation of dextropropoxyphene hydrochloride (Darvon). The subject, a 29-year-old white male, was found by his wife unconscious on the floor of his bathroom, with a hypodermic syringe in one hand and a hypodermic needle on the floor.. The subject was dead on arrival of the ambulance. "There was a vague medical history of 'hepatitis' which had extended over a period of several weeks and for which he had received self-administered 'intravenous feedings'. During this interim, the subject was reported to have suffered from nervousness and vomiting. At autopsy, there were multiple recent needle puncture marks in the anticubital fossae and over the hands and ankles". Toxicologic examination revealed propoxyphene (Darvon) in the liver, brain, blood and urine (Table 5).

Table 5

Results of Analysis for Propoxyphene*

Specimen	Propoxyphene mg/100gm
Liver	17.2
Brain	6.9
Blood	0.4
Urine	0.2

* Procedure: Wallace J.E., Briggs, J.P. and Doble, E.V., A Rapid and Specific Spectrophotometric Method for Determining Propoxyphene, J. Forensic Sci., 10:179-190 (1965) .

"Residue in the hypodermic syringe and needle contained propoxyphene (Darvon). Addicts commonly employ the spherocyte pellet found in Darvon Compound capsules in making the preparation to be injected." The author concluded that "A case of sudden death due to multiple foreign body granulomata in the pulmonary arterioles caused by intravenous injection of propoxyphene (Darvon) and to sudden acute congestive heart failure has been reported."

3) In at least one case, an error in injection has resulted in a dose of dextropropoxyphene intended for a vein entering an artery. The "intra-arterial injection of propoxyphene into a brachial artery" has been reported by Pearlman, et al (1970). The 21-year-old white female secretary was attending a "pop party" and received the contents of a

65 mg Darvon capsule dissolved in approximately 10 ml of ice water into the brachial artery. This dose caused acute arterial constriction in the hand leading to ischemic gangrene of the fingertips. Heroic medical efforts were successful in preserving the fractional integrity of the hand.

4) Claghorn and Schoolar (1966) described two cases of intravenous propoxyphene abuse, both of which were established opiate users.

The first case, a 26-year-old divorced white man had been taking heroin and hydromorphone (Dilaudid) until four days prior to admission. Unable to obtain heroin, he began to take 20-24 propoxyphene capsules daily to control his withdrawal symptoms. "This patient's method of drug preparation was to dissolve the propoxyphene in cool water and filter it away from the powder binder through cotton. He would then "shoot" this dissolved drug into a vein. Reportedly, he had been carrying on this practice intermittently for two months."

The second case, a 29-year-old white man and withdrawn addict, had a history of heroin, hydromorphone and methyldidymorphomorphione HCl (Metapon).

"Prior to his present period of treatment, the patient had begun taking propoxyphene intravenously. Capsules containing both propoxyphene and aspirin (Darvon) were opened and the aspirin removed. A solution was made with cool water and the binder separated by the cotton filtration. The filtrate was then concentrated by boiling and injected. In this process much drug was wasted but the patient estimated that his largest 'habit' required 100 capsules daily."

"The experience described was one of brief initial euphoria without the pleasurable abdominal sensation noted with heroin."

5) Fisch and coworkers (1972) reported a case of pulmonary edema and disseminated intravascular coagulation after intravenous abuse of d-propoxyphene (Darvon). The 19 year old male was referred to City Hospitals from jail. "The patient was a former heroin addict who denied using heroin within the past two weeks, but admitted injecting intravenously the contents of at least seven capsules of d-propoxyphene (Darvon) 65 mg, several hours before admission.

The formulation of Darvon injected was not the pellet, which is no longer available, but rather a formulation containing dextropropoxyphene as the active ingredient and a filler con-

sisting of cornstarch, cellulose, glycerin, stearic acid and hydroxypropyl methylcellulose. The patient reported that intravenous abuse of propoxyphene was increasingly common in the incarcerated population when heroin is not readily available.

6) Intravenous Abuse of Propoxyphene

The attached memo was discovered in the "Wyamine" file at DEA. The memo is a BDAC Special Agent's description of the intravenous abuse of Darvon (Propoxyphene) and Wyamine Inhalers (mephentermine). Identifying names and addresses have been removed from this copy.

Copied from Original Document

Division of Drug Studies and Statistics

_____, Director
BDAC _____, Texas

Abuse Potential of Non Daca Drugs (Darvon and Wyamine Inhalers)

- A. When: February 15, 1967, 10:00 P.M.
- B. Where: A private residence located at _____ Street, _____, Texas
- C. Persons Involved: Ten persons were involved; three females and seven males, all negroes, ranging in age from 19 to 25 years of age.
- D. Drug Used: The Wyamine Inhalers were broken open, their contents were injected into the veins with a hyperdermic syringe; approximately one-third of an inhaler per individual.

Darvon capsules were broken open, dissolved in water and injected into the veins via hyperdermic syringe. One or two 65 mg. capsules were injected in each individual.

- E. Apparent Effect: When the contents of the Wyamine Inhalers were injected into the veins of the individuals, they showed only slight dizziness and no comments were made with the exception of one individual who stated "That really turns you on".

When the Darvon solution was injected into the arm of one of the individuals, she stated that it made her head hurt and made her slightly nauseated. Extreme dizziness was apparent as the individual needed assistance in remaining standing. One of the individuals stated that he could get as good a feeling out of Darvon as he could from using Heroin. The length of effect was not noted.

F. Remarks: On February 15, 1967, while conducting an investigation regarding illegal sales of controlled drugs, Agent _____ had occasion to be at an apartment occupied by _____, Texas, where a large group of known addicts and pill heads were known to hang out.

The above individuals had gotten together for a party and to "get high". Later on in the evening at approximately 10:00 P.M., three "Wyamine" inhalers were produced by one of the unknown individuals and the contents were injected into the arms of the three females and two of the unidentified males, via a makeshift syringe, an eyedropper with a needle on the end of it.

After approximately thirty minutes, when the effects from the inhalers apparently began to wear off, _____ asked one of the unidentified individuals if he had any Darvon. One of the individuals produced approximately 12 capsules of Darvon. One of the unidentified individuals then dumped a capsule of Darvon in a spoon and placed a few drops of water with it and mixed the compound into a solution which he drew up into the makeshift syringe and proceeded to inject it into the arms of one of the unidentified individuals. This process was carried out on each of the individuals present. Two of the individuals present injected two capsules each.

One of the individuals tied off the arm of _____ and inserted the syringe into one of her veins. He injected a small amount of Darvon solution into her arm before the necktie used to tie off her arm was released. She instructed him to shoot it in, a small amount at a time, which he disregarded and injected the entire amount into her arm at one time. She immediately became very dizzy and needed assistance to remain standing. She started shaking her head and stated, "It hurts". The individual who injected the Darvon into her arm, told her to shake her head real hard which she did. In approximately thirty seconds she stated that it had quit hurting and that she felt good.

During conversation with _____ later on in the evening, he told Agent _____ that the Darvon compound affected him in the same manner as Heroin did. He stated, "I can get just as much kick out of Darvon as I can 'smack'. Smack is a term used among addicts meaning Heroin.

During further questioning of _____ by Agent _____ he stated that you could shoot the regular Darvon but you could not shoot the Darvon compound 65 as it contains 'acetyl salicylic acid'. He stated that in the compound 65, he had to remove the small ball which contains the compound 65 and that you could shoot it but that you could not shoot the remaining portion of the capsule.

Retyped January 1976, by M.M. This is a true copy.


Robert P. Zendzian, Ph.D.

1/5 8/76

c) Abuse--General

1) The conclusion from Patterns of Propoxyphene Abuse by Chambers and Taylor (1971) is quoted in full:

"This pilot study had delineated six patterns, with a total of nine types of propoxyphene abuse; as a drug of preference, as a drug of change experimentation, as a drug of spree abuse, as a drug of substitution, as a drug of self-treatment and as a drug for simultaneous abuse. While the authors are aware that the study was not a definitive one, propoxyphene was found to be abused by hard-core narcotic addicts, as well as those who had never abused any other drug. The drug was being abused as little as only once, sporadically for five years and as much as daily for almost two years. Propoxyphene abuse was recorded for persons as young as 15 and as old as age 60; for both Blacks and Whites; for males and females; and among persons from all of the socio-economic classes.

Replicating earlier reports, some of the abusers reported experiencing a psychic craving for the drug, the producing of

euphoria both orally and by injection, and the developing of both tolerance and dependency on the drug. Some cross-tolerance at high doses was reported, but most heroin addicts tended to discount this possibility. Suicide attempts by toxic overdose with propoxyphene were isolated.

The primary source of the propoxyphene which is being abused in the United States is over-prescription; physicians who write prescriptions for a large number of capsules. It was also noted that propoxyphene, although legally manufactured and distributed, is available on the illicit drug market in cities throughout the United States.

One of the major factors in propoxyphene abuse is unquestionably its ready availability. As with numerous legally manufactured drugs, e.g., the stimulants and the sedative-hypnotics, propoxyphene is accessible everywhere, and the knowledge of its abuse potential is diffusing in several strata of the population. It seems logical, therefore, that the dispensing of the drug should be more rigidly controlled. While additional controls will not alleviate the abuse of a drug, it should assist the process."

2) Sturner and Garriott (1973) reported 41 cases of deaths involving propoxyphene during 1970 and 1971 investigated by the

Dallas County Medical Examiner's Office. Their summary is quoted in full:

"Forty-one deaths occurred involving propoxyphene hydrochloride (Darvon) during a two-year period. Ten patients died from propoxyphene intoxication alone, while 12 were victims of a propoxyphene-alcohol combination, the latter number being identical to the deaths from a combination of barbiturates with alcohol seen during the same period. Five young women died from an ingestion of propoxyphene following an 'argument.' Four patients could be categorized as 'drug abusers' due to historical circumstances. The high levels of propoxyphene suggested habituation in three instances. Physicians should be alerted to the potential deleterious effects of indiscriminate use and abuse of propoxyphene, and should warn their patients not to drink alcoholic beverages when taking propoxyphene. They should use extreme caution when prescribing it to those in the younger age group."

3) Porter and coworkers (1973) reported on drug use in Anchorage, Alaska, the results of a survey of 15,634 students in grades six through twelve during 1971. Dextropropoxyphen (by the trade name Darvon) was included in their survey when a preliminary trial of their questionnaire resulted in a large number of write-ins of the drug. Their summary is quoted in full:

"Of all public school students surveyed by a one-page questionnaire, 36.3% reported experimentation with a drug other than alcohol or tobacco, 19.8% reported use ten or more times, and 4.5% reported frequent current use. High figures for an elementary school population indicated that 14.6% of sixth graders had used a drug other than alcohol or tobacco. Alcohol, tobacco, marihuana, solvents, nonprescription stimulants, and hashish were the most commonly reported drugs for all students. Marihuana use was correlated with use of other drugs. Most drugs showed increased usage rates compared to previous investigations, with marked increases noted for hashish, mescaline, and propoxyphene hydrochloride. Usage rates were approximately equal for boys and girls, and increased as grade level increased. Racial differences in usage were noted."

d) Darvon Field Surveys

June 27, 1969 to August 1, 1969
January 1, 1971 to March 17, 1972

The Office of Compliance Investigations of BNDD conducted two field surveys of Darvon. The first covered the period June 27, 1969 to August 1, 1969 and the second covered the period January 1, 1971 to March 17, 1972. These surveys were understandably incomplete insomuch as the drug is not under control and reporting is not required by law. The result is that the information obtained is spotty and often incomplete. Thus, the material can be expected to minimize the problem by underestimating to unknown degrees different aspects of the situation.

These surveys have shown the outlines of a pattern of abuse related incidents involving Darvon, which included poisonings, suicides, attempted suicides, accidental ingestions, thefts, possible dependence, the appearance of Darvon in arrests and seizures and the sale of Darvon on the street. The high points of these surveys are noted below.

1) Arrests and Seizures

A total of 262 cases in the first survey and 342 cases in the second survey were reported. Most of these cases

involved the finding of Darvon in possession of an individual arrested for some other reason. Two cases reported during the first survey were for "dispensing." During the second survey two cases of diversion, five of sale and two of forged prescription were reported.

2) Suicides and Injuries

Local hospitals, poison control centers, county and state medical examiners and toxicologists were queried on cases of ingestion (overdose) and death involving Darvon. The first survey reported 994 ingestions of Darvon which resulted in 56 deaths. A large number of these cases were suicidal either attempts or successes. This survey included data from 1967, 1968, and 1969. The second survey reported 924 ingestions of Darvon which resulted in 267 deaths. This survey included data from 1970 and 1971.

3) Thefts

In the first field survey, only Region 13 reported thefts of Darvon from five pharmacies and one physician's office. In contrast in the second survey, eight regions report thefts of Darvon from 56 pharmacies, one distributor and four practitioners which totaled 124,404 dose units. Although part of this new figure may be due to more and better reporting of the theft of uncontrolled

drugs, this is not a small amount of drugs and undoubtedly the number of cases reported is still less than those thefts of Darvon that occurred.

4) Miscellaneous Information

In the second survey, six regions reported street prices for Darvon (\$0.25 - \$1.50 per capsule) while the first survey produced no information on street prices.

e) Drug Abuse/Injury Reports

The data from 50 drug abuse/injury reports relative to Darvon collected by the FDA during 1968 and 1969 are tabulated in this section.

NO.	AGE & SEX	PAST HISTORY OF DRUG ABUSE	DARVON DOSAGE	ABUSE OR DEPENDENCE	REMARKS
1	F		Not Given	Abuse	Victim succumbed to a self-administered overdose of drugs. Autopsy disclosed presence of 1.2 mg. Mellaril, 0.5 mg. Darvon, and 0.143 mg. alcohol.
2	M 38		Not Given	Abuse	Victim died from overdose of Darvon-- Also under the influence of alcohol.
3	M		Not Given	Abuse	Syringe and needles relinquished, found to contain d-propoxyphene
4			6 pellets dissolved in water and injected	Abuse	Two individuals, inmates in jail, abusing Darvon. Report states other institutions freely distributed Darvon to inmates.
5	F		Not Given	Abuse	Victim died - reported by St. Joseph Hospital, Atlanta, Ga.
6	F		Not Given	Abuse	Reported by Maryland Poison Control Center
7	F		Not Given	Abuse	Individual hospitalized - Reported by Maryland Poison Control Center
8	M	Extensive history of drug & alcohol abuse	Not Given	Abuse	Suicide victim. Darvon 2.8 mg. per cent (Liver) and phenobarbita 1.4 mg. per cent (blood)
9	F 50		Not Given	Abuse	Reported by Maryland Poison Control Center - also involved Seconal
10	F		Not Given	Abuse	Reported by USN Hospital, Portsmouth, Va.

AGE & SEX	PAST HISTORY OF DRUG ABUSE	Darvon Dosage	ABUSE OR DEPENDENCE	REMARKS
F		Not Given	Abuse	Victim Hospitalized - Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
F		Not Given	Abuse	Reported by Maryland Poison Control Center
M 58		Not Given	Abuse	Reported by Maryland Poison Control Center
F-19		Not Given	Abuse	Reported by Maryland Poison Control Center
F-16		Not Given	Abuse	Reported by Maryland Poison Control Center
F-22		Not Given	Abuse	Reported by Maryland Poison Control Center
M-18		Not Given	Abuse	Reported by USN Hospital, Portsmouth, Va.
		Not Given	Abuse	Reported by Maryland Poison Control Center

No.	AGE & SEX	PAST HISTORY OF DRUG ABUSE	DARVON DOSAGE	ABUSE OR DEPENDENCE	REMARKS
4	F-44		Not Given	Abuse	Reported by Maryland Poison Control Center
5	M 21		Not Given	Abuse	Reported by Maryland Poison Control Center
6	M 18		Not Given	Abuse	Reported by Maryland Poison Control Center
7	F 25		Not Given	Abuse	Reported by Maryland Poison Control Center
8	F		18 capsules, 65 mg. each	Abuse	Victim became cyanotic 10 min. after admission to hospital & suffered 4 brief Grand Mal seizures of 15-30 min. duration each, followed by respiratory depression.
9	M		20	Abuse	Individual hospitalized after ingesting illegally obtained Darvon
10	F	Alcoholic	6 pulvules	Abuse	Victim treated in hospital emergency room and admitted to hospital.
11	F		Not Given	Abuse	Victim died after Darvon ingestion. This was a schizophrenic.
12	F 20		Not Given	Abuse	Autopsy revealed victim died from overdose of Darvon and Tincture of Opium.

NO.	AGE & SEX	PAST HISTORY OF DRUG ABUSE	DARVON USAGE	ABUSE OR DEPENDENCE	REMARKS
33	F 24		20 pulvules	Abuse	This female was treated in the Hospital emergency room.
34	F 19		Not Given	Abuse	Admitted to hospital suffering from overdose of Darvon and Allcrest.
35	M 26		10 pulvules	Abuse	Also ingested 24 aspirin tablets - patient hospitalized 1 day.
36	F 15		12 pulvules	Abuse	Attempted suicide - also took "Red pills" apparently a barbiturate.
37	F		Not Given	Abuse	Victim ingested Darvon and Librium with alcohol. Hospitalized in comatose state
38	M		Not Given	Abuse	Drug seized during permissive search of personal effects.
39	M		Not Given	Abuse	Found during inventory of personal effects - Maolate also found.
40			1000 mg. daily for 2 yrs.	possible dependence	This report states 4 patients developed dependence to Darvon. Three patients developed seizures when the drug was ingested in toxic amounts.
41	19 to 25		1 or 2 pellets	Abuse	3 females & 7 males injecting contents of tyamine inhalers Darvon. Witnessed by an agent.
42			Not Given	Abuse	Attempted suicide using Darvon & Librium.
43					AMA Reports of Adverse Reactions
44	F		Not Given	Abuse	Death due to Darvon

NO.	AGE & SEX	PAST HISTORY OF DRUG ABUSE	DARVON DOSAGE	ABUSE OR DEPENDENCE	REMARKS
45	M 58		Not Given	Abuse	Death due to Darvon Ingestion
46	F 62		Not Given	Abuse	Toxicology report revealed barbiturate level of 4.8 mg. % and Darvon 0.2 mg. %
47	F 18		Not Given	Abuse	Toxicology report revealed alcohol of 0.207 mg. % - Darvon 0.8 mg. %
48	M 68		Not Given	Abuse	Victim died ingesting alcohol 325 mg. % and Darvon 0.8 mg.
49	M				Darvon seized during an arrest (11 capsules) among other
50					Darvon among evidence submitted to New York Regional Lab.

f) Abuse -- FDA Reported

In the period from the time of marketing through August 1, 1969, the FDA has received a total of 160 reports from the manufacturer of dextropropoxyphene relating to drug dependence. These reports are discussed in a memorandum dated June 12, 1970 from Dorothy S. Dobbs, M.D., Director, Division of Neuropharmacological Drug Surveillance, FDA to Edward Lewis, Jr., M.D., Chief, Medical Officer, BNDD. The memorandum is incorporated in full in this report.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Date: June 12, 1970
Reply to: BD-220
Attn of:
Subject: Darvon
To: Edward Lewis, Jr., M.D.
Chief Medical Officer
Bureau of Narcotics and Dangerous Drugs

I note that Darvon is scheduled for discussion at the next meeting of the Scientific Advisory Committee, i.e., June 19, 1970.

You may recall, that at the time of the December 1969 meeting, I presented, verbally, a summary of the reports received by us from the manufacturer relating to drug dependence. These covered the period from the time of marketing to August 1, 1968. There was a total of 146 reports, some of them covering more than one individual. Reports included smoking the dextropoxyphene, injecting the dextropoxyphene intravenously, use of five to six Darvon Compound-65 Pulvules at a single ingestion for "kicks", and increases in dosage on the part of patient who had received the drug for legitimate purposes. In the latter group dosages ranged up to over 1000 mg. a day. Withdrawal manifestations were not frequently mentioned although in some instances one might assume that the drug was never stopped.

Attached you will find a review of reports of acute overdosage (not covered in the figures cited above) and of drug dependence or abuse; these reports cover the period August 1, 1968 to August 1, 1969.


Dorothy S. Dobbs, M.D.
Director
Division of Neuropharmacological
Drug Surveillance
Office of Marketed Drugs
Bureau of Drugs

cc: CD(BD-200)
DND(BD-220)
CD(BD-100)
CD(BD-1)

Attachment to Memo (retyped to allow reproduction)

DARVON (propoxyphene)

REVIEW OF REPORTS OF ACUTE OVERDOSAGE AND DEPENDENCE

These reports cover the period August 1, 1968, to August 1, 1969.

Acute Overdosage:

Darvon 32 mg.	1 fatality - 80 pulvules
Darvon 65 mg.	9 fatalities
Darvon with ASA	1 fatality - 20 pulvules
Darvon Compound	1 fatality 2 cases acute overdosage with recovery*
Darvon Compound 65	12 fatalities (10 adult, 2 pediatric) 5 cases acute overdosage with recovery

* Acute overdosage ordinarily implies either accidental ingestion by children or ingestion of very large doses by adults with presumed suicidal intent. With Darvon, such cases also include ingestion or injection of large doses for purposes other than suicide. These cases are, therefore, reviewed individually.

- (1) age, sex, dosage not stated; overdosage resulted in status epilepticus, respiratory and cardiac arrest.
- (2) 62 year male, NJP, "ingested about 6 capsules of Darvon Compound over a 3 to 4 hour period (normal dose 1 to 2 capsules), then drank 6 to 8 ounces of whiskey. Patient has no memory for events that followed, but was told that he discharged a firearm illegally." The

underlying condition is described as "severe headache."

- (3) An enlisted man from Ft. Leonard Wood "has been ingesting overdoses of Darvon Compound." No further information is provided.
- (4) An 18 year male, RLB, ingested "22 pink pellets" from Darvon Compound 65 capsules to "take a trip"; he is also reported to have had two beers "in a psychedelic environment." The ensuing events included convulsions and the necessity for cardiopulmonary resuscitation and IV Nalline. Patient presumably recovered.
- (5) 23 year male, P.O., injected I.V. 6 capsules of Darvon Compound dissolved in water and "felt high and elated for five hours." An abscess developed at the injection site. There is no diagnosis listed as a reason for administration of the drug.
- (6) 20 year female, C.H., ingested 35 spherules from Darvon Compound 65 in a suicide attempt. She developed respiratory depression leading to cardiopulmonary arrest, nausea and vomiting, and generalized seizure. Treatment is not stated but the patient recovered.
- (7) 21 year female, D.N., injected intra-arterially an unstated amount of Darvon Compound 65 for "kicks." Ischemia with necrosis of fingers and forearm ensued.

Dependence:

As with previous annual reports, the firm makes a classification of such reports into Chronic Overdosage, Dependence, and Dependence Questionable. The firm's classification is used.

	<u>Chronic Overdosage</u>	<u>Dependence</u>	<u>Dependence Questionable</u>
Darvon 32 mg	none stated	0	0
Darvon 65 mg	none stated	3*	1*
Darvon with ASA	none stated	0	0
Darvon Compound	none stated	0	0
Darvon Compound -65	$\frac{2^*}{2}$	$\frac{6^*}{9}$	$\frac{2}{3}$

* Totals have been corrected to coincide with case reports submitted. Each report is individually summarized.

Chronic Overdosage -- Darvon Compound 65

(1) 19 or 20 year male at US Naval Hospital for multiple war wounds is reported to have developed lethargy, tachycardia, skeletal muscle weakness, and depressed respirations. The report is ambiguous but includes the following: "Ingestion of 17-65 mg Darvon Compound 65 mg caps." Intermittent overdosage is implied but not stated.

- (2) Male patient, age not stated, suffering from painful discogenic disease, has taken Darvon Compound 65 for 6 years and recently increased dosage to 18/day. (1170 mg propoxyphene/day). He developed hallucinations after acute withdrawal.

Dependence -- Darvon Compound 65

- (1) Alcoholic male, T.F.; who reported himself "addicted to Darvon." He was hospitalized for withdrawal. Report is unclear and a maximum dosage is not stated.
- (2) Male, L.K., 31 year attorney who received Darvon for minor aches and pains and found it gave him "emotional relief and relief of anxiety." A prescription for Darvon Compound 65 was "parlayed" to a consumption of 30-65 mg Darvon capsules/day for 5 months. Reporting physician saw him following an auto accident. Patient hospitalized. Tachycardia 130-140 persisted accompanied by anxiety and walking around room "wildly." By inference, the reported physician believed his patient physically dependent. He cited "misleading" information in the PDR and recommended limitations on prescription similar to those on barbiturates.
- (3) 38 year female, N.B., used 4-5 Darvon Compound 65/day and found them "a more effective tranquilizer than

sedatives or tranquilizers." The drug was not being used for pain relief.

- (4) A report of an AF Captain of an unstated number of troops in Germany "who are smoking Darvon powder mixed with tobacco. This allegedly makes them high."
- (5) 40 year female who took 8 capsules Darvon Compound 65/day for an unstated period for headache; also termed "psychic dependence."
- (6) Female, age not stated, who took 8 capsules Darvon Compound 65/day for an unstated period for headache; also termed "psychic dependence."
- (7) 39 year female, S.H., reported by the Institute for Alcoholism and Narcotic Addiction, Philadelphia. The disorder is stated to be "pelvic surgery"; the patient is also described as suffering from "long-standing psychiatric difficulty." The patient's dosage is listed as 2300 mg./day. The duration is not stated nor is there comment on withdrawal.
- (8) 58 year male, B.C., who initially received Darvon Compound 65 for headaches. He continued the Darvon for 6 years and increased the dosage to 10 capsules/day for one year. Abrupt withdrawal resulted in "mental confusion and marked restlessness, with suggestive

delusion for about 5 days."

Dependence -- Darvon 65

- (1) Four patients from Westhaven, Conn. Va H "became dependent" on Darvon while taking greater than 1,000 mg daily. "Three of the four patients experienced toxic psychosis and seizures. One patient developed a significant withdrawal reaction when the medication was stopped . . . all four patients were receiving the drug for chronic, intractable pain problems."
- (2) 70 year male, formerly addicted to Demerol and codeine, received Darvon 65 in usual doses for several years for "chronic pain in legs." During a 6 months period the patient's dose was 20 capsules/day (1300 mg). The patient was hospitalized and medication discontinued; he had a broad based gait, confusion, and loss of memory. He was also taking large amounts of APC's.
- (3) Incomplete Report -- male patient, P.S., "taking large doses" of Darvon 65 per day -- 18 to be exact. No further details.
- (4) 22 year female with a history of "many operations" has been on Darvon for a period of 4 years. The dosage is noted as 130 mg /24 hours in the description and

130 mg /4 hours elsewhere on the case report form.

Her physician stated there "may be definite psychic dependence . . ."

SUMMARY: Although lacking in complete details, these reports add further evidence to demonstrate that Darvon is subject to abuse and that it may result in psychological and physical dependence.

g. NATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTERS, DEXTRO-PROPOXYPHENE SELF-POISONING DATA

The National Clearinghouse, a unit of the FDA, receives individual case reports of self-poisoning voluntarily submitted by poison control centers located throughout the United States. All reports of dextropropoxyphene (Darvon) poisoning for the period June 1971 through December 1971 were reviewed and these cases fitting the following categories were extracted. The category numbering system is that utilized by the National Clearinghouse and in each case self-poisoning refers to the self-administration of a greater than therapeutic dose to achieve a non-therapeutic effect.

Category 2. A deliberate act of self-poisoning for abuse purposes (i.e. for euphoria, kicks, high, etc.).

Category 5. A deliberate act of self-poisoning by individuals using the drug to gain relief from an unpleasant or uncomfortable experience (i.e. death in the family, anger, drudgery of daily existence, pressures of work, etc.).

Category 6. A suicide attempt.

This information is summarized in Table 6.

Table No. 6 Dextropropoxyphene self-poisonings reported to the National Clearinghouse for Poison Control Centers during the period June 1971 - December 1971. Twenty-four of the sixty-seven cases involved at least one or more other drugs.

-99-

Category	2	5	6	Total
Number of cases	3	28	36	67

h. Division of Hazardous Substances and Poison Control,
Dextropropoxyphene Deaths from Poisonings

The Division of Hazardous Substances and Poison Control of the FDA receives copies of death certificates of cases of death by poisoning from the medical examiners of 34 states. Their files for 1971 and 1972 were reviewed and data on deaths by overdose of dextropropoxyphene were extracted.

Table No. 7 presents deaths due to accidental overdose of self-administered dextropropoxyphene for 1971 and 1972.

The deaths of subjects Nos. 8, 10, 19, 33, 36, 37, 39, and 49 are obviously the tragic deaths of children taking an adult's medicine. The other 47 deaths are harder to classify by motive, these teenagers and adults took an excessive amount of dextropropoxyphene and died. They probably knew they were taking an excessive amount of dextropropoxyphene and they were not taking it for relief of physical pain. There is no evidence that they expected or intended to die from this dose and, thus, they may be considered drug abusers. Why each individual took an excessive dose of dextropropoxyphene is not known.

Table No. 8 presents deaths due to deliberate overdose of

dextropropoxyphene for 1971 and 1972. These cases were all reported as suicides, each individual deliberately took an excessive amount of dextropropoxyphene with the expressed intent of dying and succeeded.

Table No. 9 presents 55 deaths due to dextropropoxyphene overdose which were reported in 1971 and 1972. In these cases, the reporting agency was unable to determine whether they were the result of accidental or deliberate overdose.

There are two items of immediate interest about these 257 deaths. First, that in 230 cases dextropropoxyphene was listed as the sole cause of death and secondly, that they are reported from only 34 states and thus under-report the true number of dextropropoxyphene caused deaths. As an example of the possible magnitude of under-reporting, it should be noted that while the populous western state of California reports its poisoning deaths, the eastern metropolitan area represented by New York, New Jersey and Connecticut do not.

Table No. 7 Deaths Due to Accidental Overdose
of Self-Administered Dextropropoxyphene

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
1	Nov. 21, 1971	Male	Cauc.	30	Santa Rosa, CA	71-164990
2	Dec. 23, 1971	Female	Cauc.	37	Chico, CA	71-165708
3	Dec. 12, 1971	Male	Cauc.	25	Los Angeles, CA	71-169333
4	Jan. 19, 1971	Female	Cauc.	14	Novato, CA	71-022655
5	Jan. 19, 1971	Female	Cauc.	12	Edgemont, CA	71-024785
6	Jan. 26, 1971	Female	Negro	17	Los Angeles, CA	71-050355
7	March 24, 1971	Male	Cauc.	27	San Francisco, CA	71-056519
8	Jan. 23, 1971	Female	Negro	4	Los Angeles, CA	71-035006
9	July 1, 1971	Female	Cauc.	45	Sacramento, CA	71-090475
10	April 17, 1971	Male	Negro	2	San Bernardino, CA	71-054851
11	April 14, 1971	Female	Cauc.	39	San Francisco, CA	71-068838
12	Feb. 23, 1971	Male	Cauc.	17	Los Angeles, CA	71-061945
13	Oct. 30, 1971	Male	Cauc.	22	Long Beach, CA	71-151710
14	Dec. 23, 1971	Male	Negro	22	Richmond, VA	71-037867
15	Dec. 4, 1971	Male	Cauc.	49	Richmond, VA	71-036450
16	Nov. 12, 1971	Female	Cauc.	52	Cedar Rapids, IA	71-25412
17	Aug. 11, 1971	Female	Cauc.	53	Chicago, IL	622748
18	Nov. 29, 1971	Male	Cauc.	17	Mt. Vernon, OH	085042
19	March 20, 1971	Male	Cauc.	1	Fosston, IN	12
20	June 17, 1971	Male	Cauc.	27	Cincinnati, OH	051723
21	Jan. 9, 1971	Female	Cauc.	32	Courtland, VA	71-003167
22	May 25, 1971	Male	Cauc.	48	Salt Lake City, CA	71-183043
23	Aug. 11, 1971	Female	Cauc.	53	Chicago, IL	622748
24	July 27, 1971	Female	Cauc.	44	El Paso, TX	63508

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
25	Nov. 21, 1972	Female	Cauc.	40	Ventura, CA	72-153040
26	Nov. 17, 1972	Female	Cauc.	40	Riverside, CA	72-147817
27	Nov. 18, 1972	Male	Cauc.	40	Westminster, CA	72-147114
28	March 26, 1972	Female	Cauc.	30	Los Angeles, CA	72-088419
29	April 27, 1972	Male	Cauc.	76	Newark, CA	72-072461
30	March 22, 1972	Male	Cauc.	66	San Diego, CA	72-040940
31	Feb. 15, 1972	Female	Cauc.	22	Knoxville, TN	72-005058
32	Aug. 9, 1972	Female	Negro	38	San Diego, CA	72-108620
33	Sept. 1, 1972	Female	Negro	9	San Diego, CA	72-121830
34	Oct. 10, 1972	Male	Cauc.	54	Taft, CA	72-164745
35	Sept. 12, 1972	Female	Cauc.	23	San Fernando, CA	72-167159
36	Feb. 11, 1972	Male	Negro	7	Barnwell, SC	72-001762
37	March 2, 1972	Male	Negro	2	Newberry, SC	72-007036
38	June 15, 1972	Male	Cauc.	24	Georgia	17704
39	Jan. 20, 1972	Male	Negro	3	Richmond, VA	72-001552
40	March 17, 1972	Female	Cauc.	15	Cleveland, OH	018918
41	Sept. 13, 1972	Male	----	20	Richmond, VA	72-027987
42	March 11, 1972	Female	Cauc.	41	El Paso, TX	27004
43	Feb. 21, 1972	Female	Negro	28	Chicago, IL	605904
44	March 15, 1972	Male	Negro	16	Denver, CO	3769
45	Apr. 19, 1972	Male	Cauc.	31	Tacoma, WA	8991
46	Apr. 15, 1972	Female	Cauc.	30	Woodstock, IL	72-021283
47	July 9, 1972	Female	Cauc.	52	Richmond, VA	72-021459
48	July 15, 1972	Male	Negro	16	Denver, CO	9937
49	June 21, 1972	Male	Cauc.	1	Fort Hood, TX	40699
50	June 4, 1972	Female	Negro	20	Chicago, IL	615629
51	July 7, 1972	Male	Negro	27	Houston, TX	51638
52	July 7, 1972	Male	White	23	Houston, TX	51912
53	Nov. 8, 1972	Male	Negro	30	Lorton, VA	72-035564
54	Sept. 8, 1972	Male	Cauc.	23	Evansville, IN	72-035894
55	Nov. 7, 1972	Female	Cauc.	25	Madison, WV	72-016812

Table No. 8 Deaths due to deliberate overdose
(suicidal) of dextropropoxyphene

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
1	June 11, 1971	Female	Cauc.	16	Los Angeles, CA	71-104633
2*	March 8, 1971	Male	Cauc.	36	Middletown, OH	015563
3	March 21, 1971	Female	Negro	21	Saginaw, MI	17844
4	March 4, 1971	Male	Cauc.	48	Medford, MA	11937
5	Jan. 31, 1971	Female	Cauc.	17	Dallas, TX	06085
6	May 2, 1971	Male	Cauc.	31	Dorchester, MA	18941
7	Feb. 27, 1971	Female	Cauc.	25	Minneapolis, MN	889
8	Jan. 18, 1971	Female	Cauc.	26	Memphis, TN	71-005695
9*	Feb. 23, 1971	Female	Cauc.	51	Greenwood, SC	71-004310
10	Sept. 17, 1971	Male	Cauc.	27	Indianapolis, IN	71-041768
11	Dec. 5, 1971	Female	Negro	12	Fort Worth, TX	91683
12	Oct. 9, 1971	Female	Negro	19	Cincinnati, OH	084049
13	April 6, 1971	Male	Cauc.	31	Covington, VA	71-010122
14	Jan. 18, 1971	Female	Cauc.	57	Lavernia, TX	14200
15	April 14, 1971	Female	Cauc.	59	Virginia Beach, VA	71-011675
16	April 26, 1971	Female	Cauc.	21	Chesapeake, VA	71-010995
17	July 23, 1971	Female	Cauc.	27	Muncie, IN	71-024654
18	June 27, 1971	Female	Cauc.	18	Ft. Belvoir, VA	71-021711
19*	July 11, 1971	Male	Cauc.	17	Pasadena, TX	49756
20*	Feb. 5, 1971	Female	Cauc.	37	Williamsburg, VA	71-005186
21*	March 2, 1971	Female	Cauc.	35	Indianapolis, IN	71-014034
22*	May 4, 1971	Female	Cauc.	19	Lubbock, TX	35628
23*	July 13, 1971	Female	Indian	18	Denver, CO	09716
24	July 9, 1971	Female	Cauc.	18	Philadelphia, PA	72391
25	Jan. 27, 1971	Female	Cauc.	55	Richmond, VA	71-001508
26	March 28, 1971	Male	Cauc.	39	Charlottesville, VA	71-006627
27	July 8, 1971	Male	Cauc.	16	Cincinnati, OH	059212
28	Aug. 1, 1971	Female	Cauc.	29	Nocona, TX	66714
29	Aug. 24, 1971	Female	Cauc.	28	Roanoke, VA	71-024272
30	June 22, 1971	Female	Cauc.	43	Indianapolis, IN	71-029842

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
31	Aug. 12, 1971	Female	Cauc.	39	Kokomo, IN	71-029151
32	June 15, 1971	Female	Cauc.	27	Arlington, VA	71-018377
33	May 24, 1971	Female	Cauc.	30	Houston, TX	33868
34	May 29, 1971	Male	Cauc.	24	Williamson, WV	71-007441
35*	March 14, 1971	Female	Cauc.	29	Indianapolis, IN	71-014044
36	Feb. 27, 1971	Female	Cauc.	17	Lake Forest, IL	71-007830
37	Dec. 10, 1971	Female	Cauc.	14	Delaware, OH	091451
38	Dec. 10, 1971	Male	Cauc.	43	Wilmington, OH	089673
39	Dec. 2, 1971	Male	Cauc.	24	Denver, CO	17025
40	Dec. 6, 1971	Female	Negro	14	Minneapolis, MN	4997
41	Nov. 23, 1971	Female	Cauc.	21	Alexandria, VA	71-032060
42	Nov. 30, 1971	Male	Cauc.	24	Denver, CO	15836
43	Nov. 19, 1971	Female	Cauc.	18	Corpus Christi, TX	82239
44	Nov. 16, 1971	Female	Cauc.	24	Houston, TX	80180
45	Oct. 18, 1971	Male	Cauc.	41	Williamsburg, VA	71-030640
46	Jan. 28, 1971	Female	Negro	45	Richmond, VA	71-001526
47*	Jan. 12, 1971	Female	Cauc.	43	Anderson, IN	71-001811
48*	Jan. 23, 1971	Male	Cauc.	34	Cleveland, OH	007527
49	Jan. 13, 1971	Male	Cauc.	16	Wooster, OH	014913
50	March 23, 1971	Female	----	16	Cuyahoga, OH	016970
51	March 23, 1971	Male	Cauc.	59	Dallas, GA	16525
52	March 24, 1971	Female	Negro	24	Cincinnati, OH	02782
53*	Feb. 23, 1971	Female	Cauc.	17	Royal Oak, KY	10857
54*	May 19, 1971	Female	Cauc.	52	Pittsburgh, PA	5498071
55*	April 19, 1971	Male	Cauc.	46	Cleveland, OH	025414
56	Jan. 21, 1971	Female	Cauc.	24	Fort Leavenworth, KS	71-000726
57*	July 23, 1972	Female	Cauc.	46	Seattle, WA	17513
58	July 27, 1972	Male	Cauc.	52	Harris, TX	60421
59	July 19, 1972	Female	Cauc.	48	Houston, TX	60153
60	Aug. 23, 1972	Female	Cauc.	40	Tyler, TX	62461
61	July 11, 1972	Female	Cauc.	20	Dallas, TX	49921

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
62	May 18, 1972	Male	Cauc.	16	Cincinnati, OH	044645
63*	Feb. 19, 1972	Female	Cauc.	19	Norfolk, VA	72-004482
64*	March 6, 1972	Female	Cauc.	23	Tacoma, WA	6441
65	April 9, 1972	Female	Cauc.	20	Fort Worth, TX	31248
66*	Jan. 19, 1972	Male	Negro	33	Cincinnati, OH	012382
67	March 4, 1972	Female	Cauc.	51	Newark, OH	022097
68	April 30, 1972	Female	Cauc.	20	Seattle, WA	10329
69	Oct. 26, 1972	Female	Cauc.	27	San Francisco, CA	72-149901
70	May 13, 1972	Male	Cauc.	17	Santa Ana, CA	72-065362
71*	March 13, 1972	Female	Cauc.	63	Los Angeles, CA	72-063072
72	Jan. 26, 1972	Female	Cauc.	22	Los Angeles, CA	72-062010
73	Sept. 21, 1972	Female	Cauc.	38	Los Angeles, CA	72-127704
74	July 10, 1972	Female	Cauc.	26	Columbia, CA	72-084153
75	March 7, 1972	Female	Cauc.	35	Los Angeles, CA	72-075763
76	June 17, 1972	Female	Oriental	24	Sacramento, CA	72-093022
77	Jan. 17, 1972	Female	Cauc.	45	San Jose, CA	72-029541
78	Jan. 16, 1972	Male	Cauc.	57	San Diego, CA	72-026541
79	Feb. 19, 1972	Female	Cauc.	61	Daly City, CA	72-028881
80	Feb. 16, 1972	Male	Cauc.	50	Sacramento, CA	72-039671
81	Jan. 28, 1972	Male	Cauc.	46	Los Angeles, CA	72-035263
82	March 18, 1972	Male	Cauc.	36	San Francisco, CA	72-042193
83	April 5, 1972	Female	Cauc.	30	San Francisco, CA	72-053964
84	Jan. 26, 1972	Female	Cauc.	54	San Francisco, CA	72-009896
85	Feb. 7, 1972	Female	Cauc.	64	Ventura, CA	72-071822
86	April 12, 1972	Female	Cauc.	33	Sunnyvale, CA	72-070569
87	Dec. 19, 1972	Male	Cauc.	72	Chula Vista, CA	72-168295
88	Oct. 21, 1972	Female	Cauc.	21	Los Angeles, CA	72-165492
89	Dec. 27, 1972	Male	Cauc.	54	Concord, CA	72-164642
90	Sept. 22, 1972	Female	Cauc.	19	Los Angeles, CA	72-165812
91	Nov. 11, 1972	Female	Cauc.	64	Los Angeles, CA	72-166283
92	Sept. 27, 1972	Female	Cauc.	45	Los Angeles, CA	72-166844

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
93	Oct. 1, 1972	Male	Cauc.	32	Los Angeles, CA	72-156750
94	Nov. 27, 1972	Male	Cauc.	28	So. Lake Tahoe, CA	72-154366
95	Nov. 29, 1972	Female	Negro	20	San Diego, CA	72-161345
96	Aug. 5, 1972	Female	Cauc.	13	Los Angeles, CA	72-142335
97	Sept. 13, 1972	Female	Cauc.	43	Calabasas, CA	72-145391
98	July 23, 1972	Male	Negro	42	Los Angeles, CA	72-141792
99	Aug. 10, 1972	Female	Cauc.	50	Los Angeles, CA	72-118477
100	March 26, 1972	Female	Cauc.	23	Los Angeles, CA	72-101502
101	July 15, 1972	Female	Cauc.	23	Walnut Creek, CA	72-098477
102	July 28, 1972	Female	Cauc.	29	San Diego, CA	72-111534
103	Aug. 15, 1972	Female	Cauc.	52	San Jose, CA	72-111465
104	March 18, 1972	Male	Puerto Rican	28	Philadelphia, PA	32329
-74- 105	March 13, 1972	Female	Cauc.	37	Pittsburgh, PA	25072
106	Nov. 8, 1972	Female	Cauc.	24	Philadelphia, PA	20566
107	Oct. 19, 1972	Male	Cauc.	57	Belmont, OH	074402
108*	Sept. 25, 1972	Female	Cauc.	38	Cuyahoga, OH	075282
109	Nov. 12, 1972	Male	Cauc.	24	Richmond, VA	72-034492
110	Oct. 10, 1972	Female	Cauc.	32	Pueblo, CO	72-982192
111	Aug. 16, 1972	Female	Cauc.	37	Hennepin, MN	169
112	Oct. 15, 1972	Female	Negro	16	Fairfax, VA	72-029807
113	Oct. 5, 1972	Female	Cauc.	18	Dallas, TX	73996
114	Oct. 12, 1972	Female	Cauc.	21	San Antonio, TX	72312
115	Oct. 14, 1972	Male	Cauc.	38	San Antonio, TX	72336
116	Sept. 30, 1972	Female	Cauc.	40	Denver, CO	4570
117	Aug. 4, 1972	Female	Cauc.	35	Multnomah, OR	4249
118	Oct. 19, 1972	Female	Negro	15	Emporia, VA	72-025996
119	Aug. 24, 1972	Female	Negro	26	Terre Houe, IN	72-032163
120	July 10, 1972	Female	Cauc.	17	Sacramento, CA	72-107631
121*	Dec. 3, 1972	Female	Cauc.	35	Fox Chapel, PA	11733172
122*	May 6, 1972	Female	Cauc.	38	Long Beach, IN	72-018418

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
123*	May 27, 1972	Female	Cauc.	28	Seattle, WA	12759
124	Jan. 1, 1972	Female	Cauc.	42	Norfolk, VA	72-000761
125	March 27, 1972	Female	Negro	19	Kings Mountain, NC	9153
126*	Feb. 20, 1972	Female	Indian	23	Whiteville, NC	4917
127	Feb. 15, 1972	Female	Cauc.	34	New Castle, DE	737
128	Jan. 5, 1972	Female	Cauc.	15	Norfolk, VA	72-000793
129	Sept. 24, 1972	Male	Negro	35	Baltimore, MD	72-09216
130	Sept. 9, 1972	Female	Cauc.	39	Hutchinson, KS	72-015474
131*	May 1, 1972	Male	Cauc.	22	Wichita, KS	72-008744
132	May 27, 1972	Male	Cauc.	45	Baltimore, MD	72-05124
133	Dec. 6, 1972	Female	Cauc.	17	Fredonia, KS	72-021615
134	Aug. 22, 1972	Male	Cauc.	16	Columbia, SC	72-018698
135	Nov. 26, 1972	Male	Cauc.	18	Southfield, MI	70351
136	April 16, 1972	Female	Indian	20	Reno, NV	557
137*	Jan. 15, 1972	Female	Cauc.	41	Kailua, HI	0263
138	March 28, 1972	Female	Cauc.	61	Knoxville, TN	72-008692
139	May 28, 1972	Male	Negro	28	Detroit, MI	33406
140	Jan. 9, 1972	Male	Cauc.	26	Reno, NV	176
141	Oct. 25, 1972	Female	Cauc.	20	Livonia, MI	65161
142	Sept. 15, 1972	Male	Cauc.	18	Fort Ord, CA	72-105864
143	June 26, 1972	Female	Cauc.	27	Los Angeles, CA	72-115744
144*	Aug. 14, 1972	Female	Cauc.	47	North Hollywood, CA	72-115119
145*	July 2, 1972	Female	Cauc.	60	Glendale, CA	72-114523
146	Aug. 18, 1972	Female	Cauc.	46	San Francisco, CA	72-122697
147	April 3, 1972	Female	Cauc.	52	Torrence, CA	72-102917

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*These cases involved other drugs in addition to dextropropoxyphene.

Table No. 9 Deaths due to dextropropoxyphene overdose.
 Undetermined as to whether accidental or deliberate (suicidal).

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
1	April 2, 1971	Female	White	54	San Francisco, CA	71-056736
2	Jan. 1, 1971	Female	White	51	Portland, OR	71-000892
3	June 13, 1971	Female	White	14	Taylorstown, MS	10790
4	July 12, 1971	Female	White	42	Pittsburgh, PA	6514671
5	Oct. 31, 1971	Female	White	16	Denver, CO	14197
6	Sept. 20, 1971	Female	Negro	17	Indianapolis, IN	71-041769
7	June 14, 1971	Male	Negro	44	Charleston, SC	71-011115
8	June 28, 1971	Female	White	47	Montana	16186
9	Aug. 24, 1971	Female	White	17	Colorado Springs, CO	Unknown
10	Nov. 12, 1971	Female	White	29	Los Angeles, CA	71-168373
11	Dec. 26, 1971	Female	White	27	Santa Maria, CA	6927
12	Sept. 21, 1971	Female	Negro	46	San Francisco, CA	7097-042265
13	July 11, 1971	Male	Cauc.	26	Inglewood, CA	06927
14	Sept. 1, 1971	Female	Cauc.	34	Chula Vista, CA	71-122730
15	June 2, 1971	Female	White	39	Fremont, CA	71-095029
16	March 1, 1971	Male	Negro	44	Los Angeles, CA	71-061860
17	Jan. 9, 1971	Male	White	31	San Rafael, CA	71-022721
18	Nov. 1, 1971	Female	Cauc.	65	San Bernadino, CA	71-149985
19	April 29, 1971	Male	Negro	27	Philadelphia, PA	71794
20	Aug. 27, 1971	Male	White	55	Charleston, SC	71-016653
21	Dec. 8, 1971	Male	White	24	Pittsburgh, PA	116749
22	Jan. 30, 1971	Male	White	22	Philadelphia, PA	92165
23	Nov. 19, 1971	Male	White	40	Cincinnati, OH	084505
24	Sept. 24, 1972	Female	White	48	Colorado Springs, CO	13013
25	May 7, 1972	Female	Negro	19	Philadelphia, PA	72671

Subject Number	Date of Death	Sex	Race	Age	Location	State File Number
26	Aug. 20, 1972	Female	White	28	Vancouver, WA	17315
27	April 26, 1972	Female	Negro	16	Harvey, IL	72-024650
28	Feb. 13, 1972	Female	White	51	Indianapolis, IN	72-018630
29	Feb. 10, 1972	Female	White	37	Eugene, MT	72-002410
30	Feb. 18, 1972	Female	Negro	36	Galveston, TX	10642
31	March 20, 1972	Female	Negro	27	Albany, GA	16041
32	July 21, 1972	Male	White	9	Jacksonville, NC	26545
33	July 30, 1972	Male	White	23	Ogden, TX	72-295361
34	Oct. 10, 1972	Male	White	41	Charlotte, NC	37529
35	Nov. 4, 1972	Male	Negro	16	Baltimore, MD	72-10671
36	Sept. 22, 1972	Female	White	10	Knoxville, TN	72-032183
37	Nov. 10, 1972	Female	Cauc.	23	Ewa Beach, IA	3945
38	Oct. 28, 1972	Male	Hawaiian	28	Honolulu, HI	3424
39	Sept. 28, 1972	Male	Cauc.	27	Pala Alto, CA	72-151752
40	Sept. 29, 1972	Female	White	21	Upland, CA	72-149014
41	April 1, 1972	Male	White	49	Redwood City, CA	1383
42	Feb. 22, 1972	Male	White	25	Livermore, CA	2271
43	March 13, 1972	Female	Cauc.	38	Los Angeles, CA	7097-028225
44	March 20, 1972	Female	Cauc.	45	Los Angeles, CA	7097-024138
45	Feb. 12, 1972	Male	Cauc.	14	Los Angeles, CA	72-074334
46	April 27, 1972	Female	White	36	Los Angeles, CA	7097-035722
47	Aug. 3, 1972	Female	Cauc.	67	Inglewood, CA	7097-036726
48	Aug. 15, 1972	Female	Negro	20	Los Angeles, CA	7097-050446
49	Dec. 19, 1972	Female	White	60	La Mesa, CA	10628
50	Dec. 18, 1972	Male	White	32	Washington	72-020163
51	Dec. 23, 1972	Female	White	49	Glow, KY	095640
52	Aug. 24, 1972	Female	Negro	18	Cincinnati, OH	077856
53	Dec. 31, 1972	Female	White	19	Fort Dodge, CO	72-29793
54	Jan. 2, 1972	Male	White	29	Philadelphia, PA	102912
55	Oct. 16, 1972	Female	Negro	15	Denver, CO	Unknown

VII i) Project DAWN (Drug Abuse Warning Network) Mentions of propoxyphene and 12 other drugs during the period July 1973-September 1975

Project DAWN (Drug Abuse Warning Network) is a nationwide program which has been established by the Drug Enforcement Administration (DEA) to provide for:

1. Identification of drugs currently being abused and/or associated with harm to the individual and society.
2. Determination of existing pattern of drug abuse in selected metropolitan areas and national monitoring to observe changing trends including detection of new abuse entities and new combinations.
3. Provision of data for the assessment of the relative hazards to health and relative abuse potential for substances in human experience.
4. Provision of data needed for regulatory control and scheduling of drugs of abuse.

The DAWN system was initiated as a pilot study in 1972 and expanded to essentially its present dimensions in 1973. The data presented in this section is limited to this expansion. DAWN data is collected from crisis centers, hospital emergency rooms and medical examiners nationwide on a monthly basis. The data varies in "hardness" from the laboratory-verified medical

examiner reports to physicians or patients oral statement. Despite this potential weak point, simple analysis of various drug data accumulated by DAWN reveals agreement between the known pharmacological properties of these drugs and the DAWN data on reason for use (motivation), effect of the drug and relative lethality. In utilizing this DAWN data, no attempt is made to project nationwide use of any drug or drugs, but rather a comparison is made between drugs "mentioned" in the system during the same time period.

Total DAWN mentions for 13 drugs during the period July 1973 through September 1975 were reviewed for comparability. The drugs reviewed were aspirin, propoxyphene HCl, and propoxyphene napsylate, uncontrolled analgesics; meprobamate, phenobarbital, chloral hydrate, chlordiazepoxide, and diazepam, CNS depressants controlled in Schedule IV; phentermine, diethylpropion and fenfluramine, CNS active anorectics controlled in Schedule IV; percodan, a narcotic containing combination analgesic controlled in Schedule II and heroin, a narcotic analgesic controlled in Schedule I. Aspirin is included as the prototype non-controlled analgesic having essentially the same potency as propoxyphene, but lacking traditional abuse liability as considered under the Controlled Substance Act of 1970. Percodan is included as an example of a

controlled narcotic containing analgesis preparation. Heroin is included as the prototype narcotic drug of abuse having no recognized medical use in the USA. The remaining substances are the major drugs presently controlled in Schedule IV.

The total number of DAWN mentions range in number from 127 (fenfluramine) to 50,837 (diazepam) a 400 fold difference (Table A). It is reasonable to assume that the number of mentions of each of these drugs is a function of several factors, one of the most important of which is availability. With the exception of aspirin (an OTC drug) and heroin (which has no recognized medical use in the United States), the major source of these drugs is by prescription with some small but indeterminate amount dispensed directly or obtained by theft. Thus, one may compensate in some measure for the relative availability of these drugs by expressing the DAWN data for each drug as number of mentions per million dose units prescribed during the same period of time. Prescription estimates were obtained from the IMS National Prescription Audit. The dose units prescribed range in number from 97 million (fenfluramine) to 7,097 million (diazepam), a 70 fold difference. As expected, the calculated values of mentions per million dose units prescribed (M/mD) has a significantly smaller range, from 1.2 (diethylpropion) to 10.4 (chloral hydrate), a less than 9 fold difference.

Table A

DAWN mentions for 13 selected drugs during the period July 73-Sept. 75. Frequency, relative frequency and relative toxicity analysis

Drugs & Schedule	DAWN Mentions	Dosage Unit Prescribed (Millions)	Mentions/ Mill. Doses	DAWN Deaths	Deaths/ Thou. Mens.	Deaths/ Mill. Ince.
Diazepam (IV)	50,837	7,097	7.1	921	18	.130
Heroin (I)	40,878	N/A	N/A	4,021	98	N/A
Aspirin (None)	18,624	8,182 *	2.2	471	25	.057
	-	75,523 *	0.2	-	-	.006
Chlordiazepoxide (IV)	11,641	2,498	4.7	222	19	.089
Propoxyphene HCl (None)	10,167	2,062	4.9	1,149	113	.557
Phenobarbital (IV)	7,075	1,877	3.8	737	104	.392
Meprobamate (IV)	3,965	1,539	2.6	200	50	.130
Percodan (II)	2,630	519	5.0	7	3	.013
Chloral Hydrate (IV)	1,901	182	10.4	72	38	.395
Propoxyphene Napsylate (None)	1,464	1,135	1.3	13	9	.011
Diethylpropion (IV)	523	419	1.2	1	2	.002
Phentermine (IV)	375	231	1.6	0	0	0
Fenfluramine (IV)	127	97	1.3	0	0	0

* Aspirin is a nonprescription drug and sales are extremely hard to estimate. The low figure is an estimate of aspirin sales in pharmacies by IMS and the high figure is based on an estimate of 12,000 tons of aspirin consumed per year made in Drill's Pharmacology in Medicine 1971.

With this transformation chloral hydrate, the seventh ranking drug in number of mentions, becomes first with 10.4 M/mD followed by diazepam with 7.1 M/mD.

On the low end of the scale are found phentermine 1.6 M/mD, fenfluramine 1.3 M/mD, propoxyphene napsylate 1.3 M/mD and diethylpropion 1.2 M/mD. Due to the problems in accessing aspirin use, its true position is equivocal, but it is certain to rank on the low end of the scale with its true value of M/mD as less than 2.2, but more than 0.2. Propoxyphene HCl 4.9 M/mD ranks near the middle of the range with chlordiazepoxide 4.7 M/mD and percodan 5.0 M/mD.

The relative number of mentions of these drugs can also be considered as a function of the relative severity of the drug response. One measure of the severity of a drug response is the toxicity as expressed by lethal episodes involving that drug. Medical examiners report deaths to the DAWN system and the number of medical examiner reports is presented in Table A as DAWN Deaths. Deaths involving these drugs range in number from zero to 4,021 with heroin 4,021, propoxyphene HCl 1,149, diazepam 921, and phenobarbital 737 being the highest. Expressing this data as

Deaths/thousand mentions (D/KM) makes a significant difference. Propoxyphene HCl 113 D/KM is highest, phenobarbital 104 D/KM is second and heroin 98 D/KM is third while diazepam 18 D/KM falls to eighth, reflecting its extremely low toxicity.

Expressing this data as deaths per million doses prescribed places propoxyphene HCl .557, chloral hydrate .395 and phenobarbital .392 in that order significantly higher than the remaining drugs. A detailed analysis of propoxyphene related deaths may be found in the subsequent section, Medical Examiner Reports, Project DAWN.

The reasons given by individuals for taking the various drugs are presented in Table B with the data expressed as percent to allow comparison between drugs. A pattern can be seen here with the three anorectics ranking highest in psychic effect and heroin highest in dependence, while low in suicide and unknown/no response. In suicide attempts aspirin is highest followed by drugs having a central depressant effect.

Table B

DAWN mentions for 13 selected drugs during the period
July 73-Sept. 75. Analysis of Motivation

Drugs & Schedule	Motivation in Percent				
	Psychic Effect	Dependence	Suicide Att/Gest.	Other	Unknown/ No Response
Diazepan (IV)	15.4	7.1	47.5	4.9	25.1
Heroin (I)	17.4	68.3	2.5	4.7	6.9
Aspirin (None)	8.8	1.4	57.2	7.0	25.6
Chlordiazepoxide (IV)	17.0	6.7	49.0	4.5	22.8
Propoxyphene HCl (None)	16.4	5.0	44.1	7.7	26.8
Phenobarbital (IV)	14.0	8.4	43.0	5.6	29.0
Meprobamate (IV)	17.0	6.7	45.2	5.1	26.0
Percodan (II)	30.7	13.0	30.1	6.7	19.4
Chloral Hydrate (IV)	15.4	5.9	48.2	7.5	23.3
Propoxyphene Napsylate (None)	24.0	4.4	41.8	7.6	22.2
Diethylpropion (IV)	50.1	4.2	22.2	7.3	16.2
Phentermine (IV)	53.0	3.2	18.6	7.3	17.8
Fenfluramine (IV)	55.1	1.5	23.6	3.1	16.5

VII j) Propoxyphene Abuse in the U.S. Army Europe

In 1972 Tennant reported on drug abuse in the U.S. Army, Europe. Dr. Tennant's report was based on information that he had gathered while with the Special Action Office for Drug Abuse, U.S. Army Headquarters, Europe. Propoxyphene abuse, although representing only a small proportion of hospitalizations for drug abuse (table 3), was the single largest cause of drug caused deaths. "Twenty-one deaths due to the administration of illegal drugs have occurred since the drug scene in the U.S. Army, Europe, began in 1968. These cases have all been documented by post-mortem toxicologic determination. Thirteen of these deaths were due to propoxyphene hydrochloride (Darvon) overdose."

Table 3.—Hospitalizations for Drug Abuse in the US Army, Europe*

Cause	No.	%
Opiates	35	13
Mixed drug administration	24	8
Cyanide acids		
Strophanthidin	62	17
Unknown substance	37	9
Methadone (Moronax, Great Britain)	31	8
Amphetamine	19	5
Barbiturate	17	5
PCPN	15	4
Mephadrone	13	4
Cocaine	11	3
Propoxyphene hydrochloride	3	1
Other	4	1
TOTAL	303	100

*During September, October, and November 1971.

from Tennant, 1972

In 1973 Tennant reported in detail the non-medical use of propoxyphene hydrochloride (Darvon) which occurred among American soldiers stationed in West Germany during the period 1969-71. The author's summary is quoted in full below.

"Between 1969 and 1971, the nonmedical use of propoxyphene hydrochloride (Darvon) by US Army soldiers stationed in West Germany reached epidemic proportions. The major complications observed were respiratory arrest, psychotic reactions, and physical addiction. In 13 soldiers who died due to overdose, pulmonary edema was the primary anatomical finding at postmortem examination. Physical addiction by the intravenous route in seven soldiers was limited to a maximum of 12 weeks, because propoxyphene injections have an extremely destructive effect on veins and soft tissues. Thrombophlebitis, abscesses, cellulitis, and severe sclerosis of veins developed so rapidly at the sites of injection that addiction was interrupted. Hemolytic anemia occurred in one propoxyphene addict. Control of the epidemic among soldiers required that US Army medical facilities restrict the prescribing of propoxyphene."

Propoxyphene was readily available in large quantities from refillable prescriptions, from medical corpsmen and without prescription from some German drug stores. A survey indicated that "approximately 15 to 20% of American soldiers in West Germany had used propoxyphene one or more times for nonmedical reasons.

Administration routes were oral, subcutaneous and intravenous." Thirteen soldiers died and at least 18 were successfully revived following propoxyphene caused respiratory depression or arrest (by means of narcotic antagonists "nalorphine"). All 13 deaths followed oral administration and occurred within 30 to 45 minutes. Eight of these individuals had also consumed alcohol. Numerous psychotic reactions to propoxyphene occurred and of these 15 were severe enough to require hospitalization.

Darvon HCl was preferred for intravenous use but the "pink pellet" from Darvon combinations was also used. These latter formulations were available from stock for some time after Lilly changed their formulation. (Tennant, personal communication, April 5, 1974). Tolerance and physical dependence characterized by mild abstinence symptoms developed in several patients who used propoxyphene intravenously.

In all cases reported, intravenous use was "self limited" by extensive tissue damage at the injection site.

The epidemic was finally controlled by placing restrictions on propoxyphene availability and distribution similar to those required for controlled drugs in Schedule III and IV of the Controlled Substances Act.

VII k) Recent Reports of Deaths Involving Propoxyphene
Gravey et al (1974) reported as follows;

"The authors of this study are beginning to see an increase in the abuse potential and the danger of this drug. This report is intended to present data for suicides, accidental deaths, and selected multiple drug deaths where propoxyphene has caused death or contributed to the terminal episode. This study covering a five-year period, is taken from coroners' cases from three California counties with a total population of more than ten million people. Propoxyphene was involved in 238 fatal cases during this period."

The authors present toxicological analysis of a series of these cases. Blood and liver propoxyphene concentrations are presented in 16 fatal cases where only propoxyphene was found, blood alcohol and liver propoxyphene concentrations are presented in 64 cases where only these two drugs were found and a brief history of nine selected cases are presented. The authors stated "In the nine cases analyzed in our laboratories in which the dosage was known, fatal dosage ranged from 15-65 mg/kg. In fatal cases in which only propoxyphene was found, blood levels ranged from 0.6-6.0 mg/100 ml.; liver levels ranged from 0.5-55.0 mg/100 gm."

In a personal communication to DEA (April 5, 1974) Gravey reported 11 fatal cases involving propoxyphene from the Orange County (Calif.) Coroner's Report for 1973. Three cases involved only propoxyphene and the others included other drugs. Four of the deaths were reported as accidental and the remainder as suicides.