COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SELECT COMMITTEE ON SMALL BUSINESS UNITED STATES SENATE

NINETY-SIXTH CONGRESS

FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 34

JANUARY 31, FEBRUARY 1 AND 5, 1979

SAFETY, EFFICACY, AND USEFULNESS OF DARVON AND OTHER PREPARATIONS CONTAINING PROPOXYPHENE

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, JANUARY 31, 1979

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The committee met, pursuant to notice, at 10 a.m., in room 6226, Dirksen Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senators Nelson, Morgan Baucus, Weicker, Hatch, and Hayakawa.

Also present: Gerald D. Sturges, professional staff member; Stanley A. Twardy, Jr., minority counsel; and Judith K. Hillegonds, staff assistant.

Senator NELSON. The Senate Committee on Small Business will be in order.

The Senate Small Business Committee today resumes its hearings on competitive problems in the drug industry, and during the next several days we shall be hearing testimony specifically on the safety, efficacy and usefulness of propoxyphene, an analgesic widely sold under the trade name Darvon.

Testimony by medical experts in 1970 before this committee held that Darvon, on which Americans spent $140 million in 1977, is less effective than aspirin.

Since that time, no independent, well-designed studies have offered any evidence to the contrary.

Major Federal agency actions taken since the hearings 8 years ago that affect Darvon and preparations containing propoxyphene include:

1. The Drug Enforcement Administration ordered that dextropropoxyphene be included in schedule IV of the Comprehensive Drug Abuse Prevention and Control Act of 1970, effective March 14, 1977.

The principal effect of schedule IV classification is to limit a patient to one propoxyphene prescription and no more than five refills in any 6-month period.

2. The Food and Drug Administration amended the labeling for propoxyphene-containing preparations, effective August 7, 1978, "to include a warning against their use in pregnancy and a warning about their additive depressant effect when used with certain other products that are central nervous system depressants."

3. The Pharmaceutical Reimbursement Board of the Department of Health, Education, and Welfare set maximum allowable cost (MAC) limits for propoxyphene HCL capsules, 65 mg., and propoxyphene HCL with APC (aspirin-phenacetin-caffeine) capsules, 65 mg., effective April 10, 1978.

MAC's are established for multiple source drugs for which significant amounts of Federal funds are or may be expended under HEW programs and for which there are or may be significantly different prices.

HEW estimated that setting MAC's for both forms of propoxyphene would result in a combined savings of between $1.7 and $2.1 million per year in its outpatient programs alone. (For fiscal year 1976, HEW estimated that its medicaid outlays for these two propoxyphene products totaled $4.2 million.)

Along with the agency actions that were taken, there was a promised one that was not.

When he testified on February 3, 1971, Brig. Gen. George J. Hayes, Medical Corps, U.S. Army, Principal Deputy Assistant Secretary of Defense (Health and Environment), told the Monopoly Subcommittee of a memorandum from the Defense Medical Materiel Board concerning a list of 30 drug items proposed for reclassification to "limited standard" with eventual deletion from the Federal supply catalog.

There were five analgesics on the list, including Darvon and Darvon Compound-65 (propoxyphene HCL with APC).

Darvon Compound-65 was indeed deleted from the catalog later in 1971, but Darvon was not. In reply to my letter asking details in preparation for this hearing, Vernon McKenzie, Principal Deputy Assistant Secretary of Defense, explains it was not deleted "since two services recommended retention."

He continues:

> The item was retained since propoxyphene hydrochloride, 65 mg. was never declared ineffective in a 65 mg. dose and is considered by many physicians, both military and civilian, an effective analgesic and alternative to aspirin for patients unable to tolerate aspirin, such as patients with gastrointestinal disorders, that is, peptic ulcers.

McKenzie's use of the phrase, "was never declared ineffective," puts him wide of the mark. The phrase is from the lexicon of the FDA's Drug Efficacy Study Implementation (DESI), and the report on propoxyphene HCL from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, and the FDA's conclusion based on that report had been published in the Federal Register on April 8, 1969—22 months before General Hayes testified.

The DESI study concluded that propoxyphene HCL was effective for the relief of mild to moderate pain when administered as described in its labeling guidelines.

DESI was not the issue.

The issue was set forth in the discussion portion of the Defense Medical Materiel Board's memo:

1. Medical authorities state that propoxyphene is a weaker analgesic than codeine and no more effective than aspirin in equivalent doses.

2. There is a questionable advantage of propoxyphene over much less expensive and proven analgesics.

Clearly, the issue perceived by the Board then was the relative efficacy of propoxyphene. Because it clouded this perception, the Department of Defense spent $526,050 on preparations containing propoxyphene in fiscal year 1977, and $359,690 in fiscal 1978, through central purchasing. Local purchases by individual services may have added to those figures.

Since the hearings 8 years ago, propoxyphene has been given a hard look by the experts who evaluate drugs for physicians and pharmacists. Here are three of these copyright evaluations:

1. A March 1972 monograph prepared for the formulary service of the American Society of Hospital Pharmacists declares:

> A limited number of controlled studies indicate that 65 mg. of propoxyphene hydrochloride is no more effective than 30 to 45 mg. of codeine or 650 mg. of aspirin and may be inferior to these drugs.

In a discussion of side effects, the monograph advises:

> Side effects following administration of the recommended dosage of propoxyphene include dizziness, headache, sedation, somnolence, paradoxical excitement and insomnia, skin rashes and gastrointestinal disturbances (including nausea, vomiting, abdominal pain, and constipation). Euphoria may occasionally occur.

2. In 1976, the U.S. Pharmacopeial Convention, Inc. published the National Formulary and the USP Guide to Select Drugs—a first-of-its-kind list whose "major importance to the practitioner and student is in highlighting those drugs that should receive attention and be used as preferred drugs."

Drug selection was accomplished by the Subcommittee on Scope through a system of expert advisory panels. Scope is a subcommittee of the USP Committee of Revision, whose members are elected by the members of the U.S. Pharmacopeial Convention. The Subcommittee on Scope comprised 18 physicians, 1 dentist, 1 toxicologist and 8 pharmacists.

The explanation to the guide declares:

> In summary, there are two reasons for using the drugs listed in this book: (1) They have been judged best from the standpoint of medical merit; and (2) their standards of pharmaceutical quality are generally publicly known and more readily assured.

Propoxyphene was not listed in the National Formulary and the USP 1976 Guide to Select Drugs.

3. In its chapter on mild analgesics, the American Medical Association Drug Evaluations (Third Edition, 1977), prepared by the AMA Department of Drugs in cooperation with the American Society for Clinical Pharmacology and Therapeutics, says of propoxyphene:

> On the basis of several controlled studies using single-dose assays to determine analgesic efficacy, it is estimated that the milligram potency of propoxyphene hydrochloride is about one-half to two-thirds that of codeine; 65 mg. of propoxyphene hydrochloride is no more effective, and usually less so, than 650 mg. of aspirin.

In addition to the lack of significant effectiveness over placebo, recent data have shown that Darvon has greater abuse liability than was originally believed, and leads all other prescription drugs in the United States in drug-related deaths.

Accordingly, Public Citizen's Health Research Group has petitioned HEW Secretary Califano to remove this drug from the market

as an imminent hazard. This petition, as well as a petition to the Attorney General of the United States seeking, alternatively, to place Darvon in schedule II, will be discussed at these hearings and will be made a part of the printed record.

During 1977 there were 589 propoxyphene-related deaths reported to the Drug Enforcement Administration (DEA), which collects data from only one-third of the population of this country.

For 1974–77 there have been 2,154 Darvon-related deaths reported to DEA.

In 14 of the 23 metropolitan areas for which data comparing deaths are available, this drug was associated in the first half of 1977 with more deaths than heroin and morphine combined.

These figures do not tell the whole story, however.

According to an official of the National Institute of Drug Abuse, "The most reliable studies indicate that heroin use is generally confined to those cities, whereas physicians throughout the country prescribe propoxyphene more than any other prescription painkiller, and based on the pieces of the puzzle we know about, it does appear Darvon is involved in more deaths than heroin, probably by a ratio of nearly 2 to 1." [1]

Given the lack of significant efficacy, the easy availability of painkillers superior to Darvon, and the high abuse liability, it is puzzling that this drug is one of the most widely prescribed drugs in this country, for which the medical profession, as well as Eli Lilly & Co., must take the blame.

Darvon is promoted more heavily to physicians than any other prescription painkiller. In addition, the National Academy of Sciences-National Research Council, in its review of this drug, found that:

> An obvious effort has been made to avoid pointing out that dextropropoxyphene is structurally closely related to the narcotic analgesics methadone and isomethadone, that its general pharmacological properties are those of the narcotics as a group, that poisoning produced by dextropropoxyphene is essentially typical of narcotic overdose (complicated by convulsions) and should be treated as such, and that the distinction in dependence-producing properties and abuse liability between dextropropoxyphene and various other narcotics is essentially quantitative, rather than qualitative. That this effort, unfortunately, appears to have been successful is attested to by the fact that the majority of the house staff and attending physicians who make liberal use of Darvon assume that its pharmacology is basically similar to that of aspirin or phenacetin rather than to that of the narcotics.

According to the highly respected Medical Letter, propoxyphene has been used as an alternative to aspirin.

While adverse reactions to aspirin are observed in about 5 percent of hospitalized patients, only a small fraction are serious—for example, severe gastrointestinal bleeding, interference with normal clotting processes.

"Inasmuch as propoxyphene is largely prescribed as Darvon Compound-65, which includes aspirin, the potential toxicity of aspirin is not avoided." (The Medical Letter, May 26, 1972.)

With respect to another of the 10 Darvon formulations manufactured by the Lilly Co., the Medical Letter disclosed that Darvon is

[1] Statement by Nicholas Kozel of the National Institute of Drug Abuse as reported in the Indianapolis News, Nov. 22, 1978.

also combined with acetaminophen, Darvocet-N, which, in recommended dosage (two tablets), is probably no more effective than two tablets of acetaminophen or aspirin, and is much more costly.

Propoxyphene preparations can be abused, and serious toxicity and death occur when they are taken in overdose.

Since Darvocet-N contains acetaminophen, also highly toxic in large amounts, poisoning with this combination will be more difficult to treat than poisoning with either component above. (The Medical Letter, July 20, 1973.)

The use of fixed combinations of Darvon with aspirin or acetaminophen, which accounts for the major proportion of Darvon sales, then, is unjustified and constitutes poor medical practice.

Since Darvon's analgesic attributes are inferior to aspirin, acetaminophen, and codeine and presents greater risks to the individual—as well as to society—what is the medical justification for having it on the market?

There appears to be none, and unless compelling evidence from independent sources is presented that Darvon and its combinations are medically necessary for an identifiable group in our population, these drugs should be removed from the market.

Referring to second-rate drugs, the renowned pharmacologist, Dr. Walter Modell, said:

> But they also do harm by their very existence in the drug market. I take the stand that, as a general principle, everything that adds to the difficulty in dealing with and understanding drugs also makes drugs more dangerous. Thus, the excessive number of needless drugs constitutes a present danger. We can make the useful drugs both less dangerous and more efficient by weeding out the useless, the ineffective and the duplicates, and by so doing, make it possible for the physician to learn in depth about the potent drugs he will prescribe for his patients. We must add only those new drugs that really add something more than their mere presence.[1]

Darvon is an excellent example of a relatively ineffective, hazardous, expensive, unnecessary, and second-rate drug.

The committee has received a letter from Senator Pressler, of South Dakota, stating he cannot be present today, and this letter will be made a part of the record.

[The document follows:]

U.S. SENATE,
Washington, D.C., January 31, 1979.

Hon. GAYLORD NELSON,
Chairman, Small Business Committee.

DEAR SENATOR NELSON: This letter is to advise that I will be absent from all or at least portions of the Small Business Hearings this morning at 10 a.m. due to my attendance and participation in the Budget Committee meeting scheduled at the same time.

Please have the clerk of the committee enter this into the official record.

Sincerely,

LARRY PRESSLER,
U.S. Senate.

Senator NELSON. Is there any committee member who wishes to make a statement?

Our first witness this morning is Dr. Sidney M. Wolfe, M.D., director, Health Research Group, Washington, D.C.

Your statement, Dr. Wolfe, will be printed in full in the record.

You may proceed to present it however you desire.

[1] Drug Industry Antitrust Act, hearings on S. 1552, pp. 320–321. Testimony of Dr. Walter Modell.

STATEMENT OF SIDNEY M. WOLFE, M.D., PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

Dr. WOLFE. Thank you for the invitation to discuss our petitions to ban or severely restrict the use of propoxyphene, most commonly known as Darvon.

In the November petitions, we pointed out that Darvon led all other prescription drugs in the annual number of drug deaths, and, as was pointed out by N. Kozel of the National Institute for Drug Abuse, Darvon is probably related to even more deaths per year than heroin and morphine combined.

Since the original petitions, we have obtained more information, particularly about the toxicity in animals and humans of propoxyphene and especially its main metabolite, into which the body changes it, nor-propoxyphene.

We have also learned that a substantial portion of Darvon deaths are not due to suicide but are accidental and often occur in people chronically using the drug for pain or, in some cases, for its euphoric effects.

When people use propoxyphene, the drug is metabolized by the liver to nor-propoxyphene.

the metabolite nor-propoxyphene, because the person did not live long it takes to get to half the maximum concentration in the blood), is only 12 hours, the main metabolite, nor-propoxyphene, stays around much longer, having a half-life of 38 hours.

Because of this long half-life, people using Darvon on a chronic basis accumulate large amounts of the metabolite nor-propoxyphene in their blood.

Much of the early human toxicology on propoxyphene looked just at blood levels of the drug itself and unless the blood level was one or two micrograms per milliliter of blood, or more, the death was often not attributed to propoxyphene.

In cases of suicide where death occurs shortly after ingestion of sometimes 10 or 20 pills, the blood propoxyphene level is, in fact, usually above 1 or 2 micrograms per milliliter with much lower levels of the metabolite nor-propoxyphene, because the person did not live long enough to convert the drug into the metabolite.

In chronic users, however, there is much more nor-propoxyphene than propoxyphene in the blood. Someone regularly taking as little as two pills—65 milligrams per pill—three times a day can get a blood propoxyphene level of 0.68 microgram per milliliter, but a nor-propoxyphene level of 1.2 micrograms per milliliter.[1]

A cancer patient, chronically using two 65 mg. pills every 4 hours—recommended dose in 1 pill every 4 hours—just twice the recommended dose, had a propoxyphene blood level of 0.87 microgram per milliliter and a nor-propoxyphene level of 3.1.[1]

The fact that people using Darvon at or slightly above the recommended dose can get nor-propoxyphene blood levels of 1 to 3 micrograms per milliliter is particularly alarming in view of the following findings:

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[1] Verbeley and Inturrisi, J. Chromatography 75:195, 1973.

(a) In many cases of accidental death due to Darvon, the blood nor-propoxyphene levels are in this 1 to 3 micrograms per milliliter range with propoxyphene levels much lower, often less than one, as in the patients cited above.[1] This is different than one would see in the suicide cases.

(b) Comparable blood levels, 1 to 3 micrograms per milliliter, of nor-propoxyphene in animals can cause significant blocking of conduction through the heart, a toxicity which can lead to arrhythmias and death.

Although the medical literature, because of people who had taken Darvon and developed toxicity, as long as 15 years ago, contained many cases of Darvon poisoning in which patients had abnormal electrocardigrams showing an inhibition of electrical conduction through the heart and although many Darvon deaths were said to be of cardiac origin, the first animal study on the cardiac toxicity of propoxyphene and nor-propoxyphene was not done until 1976 by the major manufacturer, Eli Lilly.

From a source within Lilly, we have obtained an 11-page progress report of dog experiments, dated February 16 to August 15, 1976.

On March 17, 1977, a short one-half page abstract of this study—omitting critical information—was sent by Lilly to FDA with a note that "a complete presentation of this data will be submitted in a manuscript that is now being prepared."

As of several weeks ago, when I forwarded this report to FDA and almost 2 years after Lilly's promise to FDA, the "complete presentation" had not been sent to FDA by Lilly nor has it ever been published. A stamp on the top of the report says it should "not be published or disclosed to unauthorized persons without the specific written permission of Dr. I. H. Slater."

The half-page abstract was published, but it does not contain important information in the study provided to us from sources inside of the company

Whereas, on a legal technicality, apparently consideration is being given to reprimanding the company for this.

A stamp on top of the report, without specific permission of Dr. Slater, was put on it, and also it mentions it should be kept locked up.

I think it is an interesting commentary that the company decides to keep to itself, for all practical purposes, critical information about a drug so widely used which the company sells, and makes a fortune from.

The study showed that both propoxyphene and nor-propoxyphene could cause inhibition of cardiac electrical conduction in the 1 to 3 micrograms per milliliter range and that nor-propoxyphene was even more potent than propoxyphene in one important type of inhibition.

There is a range level of nor-propoxyphene 1 to 3 microgram range, that people using the drug on a regular basis, at or even as little as twice above the recommended dose can get in their blood.

Although the Lilly study says the blood concentrations of propoxyphene and nor-propoxyphene were "substantially higher than required

[1] Personal communcation, Dr. Boyd Stevens, coroner, San Francisco, and Dr. Larry Lewman, deputy coroner, State of Oregon.

for analgesia"—pain relief—the levels of nor-propoxyphene causing inhibition in these dogs were the same 1 to 3 micrograms per milliliter range which can be seen in people who are chronically using the drug.

For the first time in the current labeling of Darvon there is mention, 2 years after the study was done, of the possibility of cardiac conduction problems.

There is no mention of nor-propoxyphene, the fact it accumulates, or that there is evidence of this.

It just says problems can occur with the drug.

A recently published Danish study [1] also shows that nor-propoxyphene in the 1 to 3 micrograms per milliliter range in rabbits can cause significant delay or inhibition of cardiac conduction and cardiac arrhythmias also were seen.

An earlier Danish study of 11 cases of Darvon poisoning [2] showed that four patients had cardiac conduction delays similar to those described above with blood nor-propoxyphene and propoxyphene levels of:

NPX	*PX*
0.78	0.47
.39	.74
.79	.51
.35	.23

In other words, they had more of the metabolite than of the drug itself in their blood.

One of the four patients also ingested a substantial amount of alcohol, but this in itself is not known to cause the cardiac delays.

According to both Dr. Larry Lewman, deputy coroner of Oregon, and Dr. Boyd Stevens, coroner of San Francisco, most of the Darvon deaths are not suicides but accidents.

One of the criteria for making this decision is a nor-propoxyphene blood level as high or higher than the propoxyphene level, often suggesting chronic use of propoxyphene.

Blood nor-propoxyphene levels in such accidental deaths are often slightly less than 1 microgram, 1, 2, 3, or 4 micrograms per milliliter of blood with propoxyphene levels often less than 1.

The margin of safety or the therapeutic index of a drug is the ratio between the amount needed to achieve the therapeutic effect (in this case alleged relief of pain) and the amount causing toxicity.

According to Danish toxicologist, Dr. J. Simonsen [3] Darvon has a "narrow therapeutic index": He says that "just four times the ordinary therapeutic dose can produce highly serious poisoning."

The experience concerning Darvon varies from one part of the country to the other.

In North Carolina, they published studies suggesting most deaths are suicides, but even in a paper by Dr. McBay, who will testify later, one of his patients had a blood level of propoxyphene of 0.8, and a level of nor-propoxyphene of 2, suggesting in fact they had not in fact taken a huge suicidal dose, and several of their patients are also listed as accidents rather than suicide.

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[1] Lund-Jacobsen, Acta. pharmacol. et toxicol., *42*, 171, 1978.
[2] Gustafson and Gustafson. Acta. Med. Scand. *200*, 241, 1976.
[3] Ugeskr. Laeg. *137*(44) 2605–2609, 1975.

One of the criteria for making a decision it is an accident rather than a suicide, is that the metabolite level (nor-propoxyphene) is higher than the blood propoxyphene level.

San Francisco chief coroner Dr. Boyd Stevens told me that "if you double the Darvon dosage and take just one to two bar drinks, you can get into the toxic or lethal range." These remarks have to do, I would imagine, with chronic use, but they may even refer to acute ingestion.

Dr. Stevens points out that partly because of its relative weakness as a painkiller, patients may well be inclined to take two pills or more instead of one, finding that one did not work as well as they thought it would. He says, therefore that many of the Darvon accidental deaths are not abuse—in the strict sense.

This very low margin of safety is very likely related in many cases to the accumulation, as described above, of the toxic metabolite nor-propoxyphene in people regularly using the drug.

In the above-mentioned study by Simonsen, the author himself discussed the fact that we may be just seeing the tip of the iceberg as far as Darvon deaths.

The study describes two elderly people found dead with no evidence of suicide whose deaths would otherwise have been attributed to natural causes but for a Danish law requiring autopsy on those dying alone. Subsequent toxicologic analysis showed both to be Darvon deaths.

Since Darvon's effectiveness in relieving pain is somewhere between that of aspirin, or acetaminophen (as in Datril, Tylenol) and a placebo and substantially less than that of codeine (in schedule II and III), it is of interest to look at the number of deaths and the death rate of these preferable analgesics in comparison to Darvon.

Drug	Deaths, 1977 [1]	Deaths per million prescriptions [2]
Darvon	590	19
Codeine	255	5
Aspirin [3]	150	<1
Acetaminophen [3]	77	<1

[1] DAWN Quarterly Report January–March 1978.
[2] 1977 prescriptions filled from National Prescription Audit, I.M.S.
[3] 1977 retail sales of aspirin of $500,000,000 and acetaminophen, $150,000,000—assume average cost of $1 for aspirin, $1.50 for acetaminophen and use deaths per million bottles.

When the possibility of controlling Darvon by putting it into the weak control of schedule IV was first raised in 1973, Lilly responded by saying that if the drug should wind up in schedule IV, despite its protests, "we believe it wouldn't have any material effect on sales of the product." [1]

In the year before Darvon was put into schedule IV (March 1976 to February 1977), there were 459 deaths related to its use.

In the first year of schedule IV (March 1977 to February 1978), the number was 510. Although there appears to be a decrease in deaths during the latter part of 1978, these data underestimate the eventual

[1] Wall Street Journal, Aug. 6, 1973.

number of reported deaths, since all 1978 records are not completed and sent to DEA until well into 1979.

Although there has been an apparent but slight decrease in emergency room visits involving Darvon, this is not accompanied by any evidence yet of a decrease in fatalities.

Now, as far as codeine is concerned, the various studies or pharmacology books described it as being half or two-thirds as effective as codeine.

Senator NELSON. Dr. Wolfe, when you make reference to Darvon in the first sentence, are you talking about just propoxyphene, or are you talking about Darvon combinations?

Dr. WOLFE. I am talking about propoxyphene alone in comparison with aspirin or acetaminophen.

Darvon compound also has aspirin in it, and I think the preponderance of studies failed to show that Darvon plus aspirin is more effective than aspirin alone, aspirin alone being a very effective painkiller.

Senator NELSON. What studies do you rely upon for this statement relative to the effectiveness of propoxyphene?

Dr. WOLFE. I can provide a list of the studies.

They are listed in our petition to the Justice Department which we submitted to you, on the effectiveness of the drug.

[The list follows:]

FOR RELEASE TUESDAY, NOVEMBER 21, 6:00 P.M.

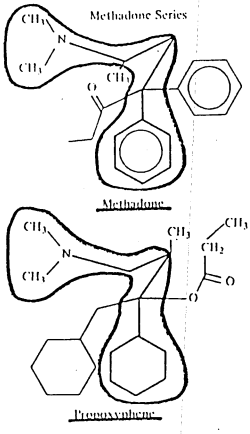
Public Citizen

November 21, 1978

Joseph Califano
Secretary
Department of Health, Education, and Welfare
Humphrey Building, Room 615-F
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Califano:

According to recent information we have obtained from the Drug Enforcement Agency (DEA), Department of Justice, the narcotic propoxyphene (as in Darvon)--closely related to methadone[1]--leads all other prescription drugs in the United States in drug-related deaths. In 14 U.S. cities (see page 3) there were more propoxyphene (DPX)-related deaths than morphine and heroin-related deaths in 1977.



SIMILARITY BETWEEN
PROPOXYPHENE (DPX)
AND
METHADONE

[1]The above figure is from the Second Edition (1978) of Clinical Pharmacology by Melmon and Morrelli, MacMillan Publishing Co., Inc., New York.

Because propoxyphene is of so little value as a pain-killer--although Americans spent about 140 million dollars in 1977 for the Lilly-manufactured Darvon drugs[1]--is so widely abused and is so lethal, I urge you to either:

a) Ban immediately the marketing of propoxyphene as an imminent hazard under the Food, Drug and Cosmetic Act, 21 U.S.C. §355(e), and make it available only as an investigational drug for treating narcotics addicts[2] or, in the alternative,

b) Support our petition[3] (see enclosure) to reschedule DPX as a Schedule II narcotic which would impose production quotas and prohibit refills of prescriptions.

The following information is excerpted from our Drug Enforcement Agency petition:

• During 1977 alone there were 589 propoxyphene (DPX)-related deaths reported to DEA from their Drug Abuse Warning Network (DAWN) which collects data from only 1/3 of the population of this country.

• In the past 4 years (1974-1977), there have been 2,154 DPX-related deaths reported to DEA. Most recently, as heroin has become somewhat better controlled, DPX-related deaths have even surpassed heroin and morphine-related deaths in many cities. In 14 of the 23 metropolitan areas for which data comparing DPX-related deaths with heroin/morphine deaths are available, propoxyphene (DPX) was associated with more deaths than heroin/morphine in the first half of 1977. The cities are Boston, Buffalo, Cleveland, Dallas, Denver, Indianapolis (home of Lilly, producer of Darvon and other propoxyphene drugs), Miami, Minneapolis, New York, Oklahoma City, Philadelphia, Phoenix, San Antonio and Seattle.

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[1] Propoxyphene is also available as a generic drug but most sales are for Lilly products including Darvon, Darvocet, Darvocet-N, Darvon-N, Darvon Compound 65, etc.

[2] DPX is currently approved by FDA as an investigational drug for treating narcotic addiction.

[3] Under the Controlled Substances Act, 21 U.S.C. §811(a), the Department of Justice is being petitioned by Health Research Group today to move propoxyphene to Schedule II.

DPX DEATH RATES IN U.S. CITIES

In order to compare various U.S. metropolitan areas in terms of DPX-related deaths, the number of such deaths for each area between July 1973 and December 1977 was divided by population (in millions) of that area. These results can be seen in Table 2.

TABLE 2

PROPOXYPHENE(DPX-AS IN DARVON)DEATH RATES FOR U.S. METROPOLITAN AREAS[a]

Rank	Area	DPX-Related Deaths (7/73-12/77)[b]	Population[d] (In Millions)	Deaths/Million People
1	Phoenix	81	1.218	66.5
2	San Francisco	189	3.129	60.4
3	San Diego	95[c]	1.588	59.8
4	Dallas	80	1.690	47.3
5	Denver	61	1.387	44.0
6	Los Angeles	276	6.945	39.7
7	Cleveland	78	1.975	39.5
8	San Antonio	37	.949	39.0
9	Miami	52	1.439	36.1
10	Buffalo	46	1.327	34.7
11	Detroit	132	4.174	31.6
12	Oklahoma City	21	.683	30.7
13	Philadelphia	133	4.797	27.7
14	Boston	72	2.731	26.4
15	New York City	274	11.316	24.2
16	Chicago	151	6.983	21.6
17	Atlanta	32	1.532	20.9
18	Washington, DC	60	2.936	20.4
19	Indianapolis	15	1.147	13.1
20	Minneapolis	20	1.846	10.8
21	Seattle	14	1.411	9.9
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a. These are the 23 metropolitan areas which have been under surveillance by the DAWN Network for at least 2 1/2 years.

b. DPX-Related Deaths(except San Diego) are from Information Systems Section of Drug Enforcement Agency, Department of Justice. Included are all deaths where drug is a contributing factor or in which a toxic level is found (or suspected because of ingestion history).

c. Deaths for San Diego are from San Diego coroner's office since San Diego did not become part of the DAWN System until mid-1975. (San Diego includes only 1974-1977.)

d. Populations of metropolitan areas are from DAWN (Department of Justice) Quarterly Report (July-September 1977).

For example, Phoenix, the leading U.S. metropolitan area--as far as DPX-associated death rates--had 81 deaths during that interval. With an area population of 1.218 million the rate was found to be 81 divided by 1.218 or 66.5 deaths per million.

At the other end of the list of metropolitan areas is New Orleans. Its DPX-death rate is 8.2 per million or less than 1/8 that of Phoenix.

● Although DPX was placed in Schedule IV by DEA in March, 1977, this appears to have had little effect on its prescribing or abuse, as has been the case with other drugs placed in Schedule IV. (Schedule IV allows a prescription to be called in over the phone and as many as 5 refills each 6 months. Schedule II would place production quotas on the manufacture of DPX, disallow oral prescriptions and not allow any refills.)

In 1977, there were 33.5 million prescriptions filled for DPX drugs, down only 9.5% from 37 million in 1976. In 1977, during the last 9 months of which DPX was in Schedule IV, there were 589 DPX-related deaths, up from 445 in 1976, before Schedule IV "controls" were imposed.

● According to a 1976 Department of Justice Report on the abuse of DPX, DPX-related fatalities outranked all prescription drugs in death-rate even when the number of prescriptions written were adjusted for. By dividing the number of drug-related deaths by the number of prescriptions, DPX (in this instance plain propoxyphene sold as Darvon by Lilly) was well ahead of all drugs including phenobarbital and valium.

In addition to evidence that DPX (mostly Lilly's Darvon products) is doing more damage than the wares of dope-pushers in many U.S. cities, it is important to analyze why doctors have made DPX so popular.

DOCTORS MISLED ON DPX EFFECTIVENESS

Originally introduced as a "non-narcotic" by Lilly in 1957, Darvon(DPX) was said by the company, to be "equal to codeine... milligram for milligram" in its pain-killing properties. At present the preponderance of properly-controlled studies fail to show that DPX is any more effective than aspirin and many show it to be less effective than aspirin, or, in some cases, no more effective than a placebo. It is clearly less effective than codeine. The other attractive feature of this "non-narcotic" was that doctors didn't need a narcotic prescription to use it. The American Medical Association book on Drug Evaluation (1st Edition, 1971) stated, of DPX, that "its popularity is probably due to the fact that it does not require a

narcotic prescription, rather than to its effectiveness as an analgesic...."

DOCTORS ALSO MISLED ON DPX DANGER

Lilly also claimed DPX had "fewer side effects than codeine" but by 1970, the respected source of drug information, The Medical Letter wrote "many physicians are not sufficiently aware that coma, circulatory and respiratory depression, convulsion and death can result from overdose with propoxyphene, that the clinical picture is similar to that seen with narcotic drugs...."

A recent survey (1977) of U.S. physicians shows that most continue to think DPX is a much less dangerous drug than other drugs, which, in fact, are involved in far fewer drug deaths than DPX.[1]

A FINE LINE BETWEEN USE AND ABUSE

In larger than recommended doses DPX produces a euphoria or "high" which makes it attractive as a drug of abuse. It is generally agreed that DPX can be addicting--albeit less so than morphine--and one study concluded that "addiction can occur under the usual circumstances of medical prescribing."[2]

The 2nd Edition of Clinical Pharmacology (1978) by Melmon and Morelli stated that "the most prominent effects (of DPX) may be its addictive quality."

The Department of Justice DAWN (Drug Abuse Warning Network) data show that among patients in emergency rooms whose source of drugs could be ascertained, over 90% obtained their DPX with legal prescriptions.[3]

NATURE OF DPX DEATHS

In a May 4, 1978 letter to FDA, Oregon Deputy State Medical Examiner Dr. Larry Lewman wrote that "propoxyphene is by far the most common cause of fatal drug overdose in Oregon."

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[1] International Journal of Addiction 12, 43, 1977.

[2] International Journal of Addiction 9, 775, 1974.

[3] DAWN Quarterly Report, July-September 1977.

He went on to say that although some DPX overdose deaths were, in fact, attempted suicides, "accidental overdoses of DPX" was the category "into which most of the DPX overdoses in Oregon appear to fall." In other words, the margin between the doses which achieve the desired euphoria and those which are harmful or even fatal is extremely narrow.

Dr. Lewman did not believe that education of physicians was adequate and suggested, in the same letter to FDA, that DPX be moved into Schedule II. (On November 7, 1978, Oregon Public Health Officer, Dr. Edward Press, redirected this request to reschedule DPX in Schedule II in a petition to the Department of Justice, Drug Enforcement Administration.)

In summary, DPX is the deadliest prescription drug in the U.S., has been related to the deaths of thousands of people in the U.S. (and elsewhere) and is even outdoing morphine and heroin in 14 U.S.cities in its relationship to drug deaths.

In my view, there are two possible courses of action:

1. Invoke the Imminent Hazard Section of the Food, Drug and Cosmetic Act, 21 U.S.C. §355(e), and immediately suspend the New Drug Application (and marketing) of DPX. If you determine that there is no legitimate use for DPX as a pain-killer or that the risks of DPX outweigh any benefits even as a pain-killer, and that the drug should therefore be eventually removed from the market, the magnitude of DPX deaths during the 2-3 years that would transpire before the "slow" banning procedures mandate use of the imminent hazard provision. The evidence of DPX-caused deaths is more than sufficient to prove that this drug is "posing a significant threat of danger to public health."

In the British Medical Journal, an editorial on the "Dangers of Dextropropoxyphene"[1] queried, "How good is the case for using the drug at all?" After discussing the lack of "hard data on its therapeutic value...compared with other analgesics", the journal goes on to say that "any doctor prescribing the drug rather than a simple, less expensive and potentially less toxic preparation should be aware of the hazards and able to justify his choice."

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[1] British Medical Journal 1, p. 668, 1977.

The one use, now under investigation, for which the benefits of DPX may outweigh its risks is in the treatment of narcotic addiction. Because DPX is a narcotic, it has been used to withdraw addicts from other narcotics, such as methadone, its close relative. Since there is in existence an Investigational New Drug (IND) approval for DPX, this use would not be altered by declaring it an imminent hazard and stopping its marketing as an analgesic.

2. Reschedule DPX in Schedule II. If you believe there is a legitimate use for DPX as a pain-killer--despite its relative ineffectiveness for this indication--it could be placed in Schedule II for those people for whom both aspirin and acetaminophen and other less dangerous analgesics were not effective or not tolerated. I do not know how large a group, if any, this might be but I would estimate that it is less than 1% of those currently using DPX. The enclosed petition to the Drug Enforcement Administration seeks this rescheduling under the Controlled Substances Act, 21 U.S.C. §811(a). This act requires that the Secretary of HEW submit an opinion to the Department of Justice concerning any proposed scheduling or rescheduling of drugs.

Although I favor the imminent hazard route and this letter constitutes our petition to ban DPX as an imminent hazard to the public health, you must decide how best to protect the American public from this deadly drug which--in addition--is wasting more than 140 million dollars a year of health care resources.

I look forward to a prompt reply.

Sincerely,

Sidney M. Wolfe, M.D.
Director Health Research Group

SMW:pm

Enclosure

NOTE: Legal and/or scientific research for the petition was contributed by Ellis Gordon, Michael Lipsett, an attorney now attending University of California, San Diego Medical School, and Deborah Schechter, staff associate of the Health Research Group. Staff researchers at the Department of Justice, Drug Enforcement Agency, were also helpful in providing data not otherwise available.

Sidney M. Wolfe, M.D. and)
)
Public Citizen Health)
Research Group)

Petitioners

TO: Honorable Griffin Bell
Attorney General of the United States; and

Honorable Peter Bensinger, Administrator
Drug Enforcement Administration, Department of Justice

PETITION REQUESTING TRANSFER OF THE NARCOTIC DEXTROPROPOXYPHENE (DARVON) AND ITS SALTS FROM CONTROLLED SUBSTANCES SCHEDULE IV TO SCHEDULE II.

I. PETITIONERS

Petitioner Sidney Wolfe is a medical doctor licensed to practice in Washington, DC.

Petitioner Public Citizen Health Research Group is a Washington-based, non-profit organization engaged in public interest research on health issues, including drug abuse.

II. AUTHORITY FOR PETITIONERS

Petitioners' authority to submit this petition derives from the Controlled Substances Act, 21 U.S.C. § 811(a), and the Administrative Procedure Act, 5 U.S.C. § 553(e).

III. THE CASE

In 1977 the Administrator of the Drug Enforcement Administration (DEA) found that the widespread abuse of dextropropoxyphene (Darvon) justified its inclusion in Schedule IV of the Controlled Substances Act. Despite the restrictions which Schedule IV places on the prescription of dextropropoxyphene, this drug continues to be widely prescribed and abused. Petitioners contend that in order to curb such abuse dextropropoxyphene must be subjected to the stringent controls of Schedule II.

Under the Controlled Substances Act, the Attorney General may by rule transfer a drug into Schedule II if he finds that: (1) the drug has a high potential for abuse; (2) the drug has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and (3) abuse of the drug may lead to severe psychological or physical dependence. 21 U.S.C. §§811, 812 (b)(2). There is substantial evidence that dextropropoxyphene (Darvon) fulfills these three criteria of Schedule II.

In addition, there is reliable medical evidence that this drug is relatively ineffective as an analgesic, the primary purpose for which it is prescribed. From a therapeutic standpoint, nothing would be lost by restricting the availability of this drug through the imposition of Schedule II controls.

Sidney M. Wolfe, M.D. and)
)
Public Citizen Health)
Research Group)

Petitioners

TO: Honorable Griffin Bell
Attorney General of the United States; and

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Drug Enforcement Administration, Department of Justice

PETITION REQUESTING TRANSFER OF THE NARCOTIC DEXTROPROPOXYPHENE (DARVON) AND ITS SALTS FROM CONTROLLED SUBSTANCES SCHEDULE IV TO SCHEDULE II.

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IV. INTRODUCTION

Dextropropoxyphene (hereafter DPX) is structurally related to methadone, a synthetic narcotic; its effects are qualitatively similar to those of narcotics. In 1956, a year before DPX was first marketed as Darvon by Eli Lilly and Company, it was reported that this drug could produce narcotic-like effects of respiratory depression, pupil constriction, and euphoria, and could reduce the severity of withdrawal from morphine.[1] Nevertheless, this narcotic analogue was introduced to physicians as a non-narcotic analgesic, equal, milligram for milligram to codeine, but without the potential for addiction and abuse of the latter.[2] As a result of DPX's being promoted as a potent non-narcotic analgesic, DPX gained such popularity that it has become one of the most commonly prescribed drugs in the United States.[3]

Despite promotional efforts of the Lilly Company to the contrary, DPX remains a narcotic, more harmful and less effective than originally believed. In larger than recommended doses it produces a euphoric "high", which makes it attractive as a drug of abuse. Side effects of DPX, such as dizziness, constipation, nausea and vomiting are typical of narcotics. High doses of DPX produce the characteristic quartet of narcotic overdose--respiratory depression, pinpoint pupils, coma, and circulatory collapse--as well as convulsions, cardiac arrhythmias and pulmonary edema.[4] The respiratory depression produced by DPX overdose can be reversed by naloxone, which is used to treat narcotic overdose.[5,6,7] Physical and psychological dependence on DPX can occur, although this dependence is not so severe as that caused by morphine.[8]

Like the narcotics heroin and morphine, DPX is deadly. From April 1975 to June 1977, (the most recent date for which reliable published comparative statistics are available), it was the second most frequently implicated drug (2nd only to heroin and morphine) in coroners' reports of drug-related deaths in large American metropolitan areas.[9]

Even the Eli Lilly Company has had to modify its public posture. By 1972, it had conceded that "propoxyphene's general pharmacologic properties are those of the narcotics as a group."[10]

Placing DPX in Schedule IV has not significantly affected the sales or abuse of this dangerous narcotic. The value of Lilly's sales (revenue to manufacturer) of 7 DPX products increased from $82,001,000 in 1976 to $82,878,000 in 1977.[11] Considering that the retail drug markup is often close to 70%[12], Americans spent nearly $140,000,000 during 1977 on Lilly-produced Darvon and Darvon combinations, even though there was a slight decrease in the total number of prescriptions. This does not include the products of the other 32 companies licensed to produce DPX. While reported abuse of DPX has not significantly increased since March 1977, neither has it declined as will be seen in the next section. This is due in large part to the ready availability of DPX--the vast majority of DPX abusers obtain the drug with legal prescriptions. This petition will show that the more stringent controls of Schedule II should be imposed on DPX in order to restrict its availability.

V. Criterion 1 - High Potential For Abuse

In determining that a drug should be included in Schedule II, it must be established that the drug has a high potential for abuse* 21 U.S.C. §812 (b)(2)(A). A drug's potential for abuse can be estimated in clinical tests such as those for opiate narcotics.

> "Assessing Abuse Potential....A drug is considered to be nonopioid with respect to abuse liability (1) if it does not suppress the opioid withdrawal syndrome when tested in subjects physically dependent on morphine, (2) if it does not produce morphine-like physical dependence when given chronically, and (3) if postaddicts neither consistently identify it as "dope"(morphine-like) nor repeatedly request it when offered the opportunity to do so. On the other hand, if a compound is found to share these key characteristics with morphine, it is considered to have a high abuse liability."[13]

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* As used herein, "abuse" refers to intentional non-therapeutic use of a drug. This included taking a drug for any of the following reasons: (1) dependence (addiction); (2) psychic effects; (3) attempted or successful suicide. See section on Legal Analysis, below, for discussion of legislative interpretation of the term.

According to clinical trials using these criteria, DPX's abuse liability is lower than that of morphine and codeine. However, ultimately the abuse liability of a drug must be evaluated in light of the prevalence of its abuse. Indeed, in determining the proper scheduling for a drug, the Attorney General is directed to consider a drug's "actual or relative potential for abuse." 21 U.S.C. § 811 (c)(1). Looking for evidence of DPX abuse, one discovers an embarrassment of riches. Prior to the inclusion of DPX in Schedule IV in 1977, there was extensive medical and statistical documentation that this drug, alone and in combination with alcohol and other drugs, was subject to both oral and intravenous abuse which resulted in over a thousand deaths between 1969 and 1975 1975.[14-26]

Reviewing the medical literature and nation-wide drug abuse statistics, a study commissioned by the Justice Department found in 1976 that:

1. Dextropropoxyphene is a centrally active narcotic analgesic (pain-killer) with a spectrum of activity qualitatively similar to morphine, the prototype narcotic analgesic.

2. Dextropropoxyphene produces a mild to moderate physical dependence of the morphine type. Unlike morphine, development of dextropropoxyphene dependence requires the administration of doses in excess of the recommended therapeutic dose.

3. Intravenous administration of dextropropoxyphene to experienced addicts produces "pleasant" morphine-like effects which cannot always be distinguished from those of morphine.

4. Dextropropoxyphene has properties which lead individuals to self-administer either orally or intravenously excessive amounts of the drug.

5. Tolerance develops to the "pleasant" effects of dextropropoxyphene as well as to other effects so that individuals can ingest or inject doses of the drug which would be in the lethal range for nontolerant individuals.

6. Self-administration of dextropropoxyphene in increasingly higher doses for the reasons noted in No. 3, 4, and 5 has produced physical dependence.

7. Intravenous self-administration of dextropropoxyphene in man utilized the pellet formulation of Darvon which is no longer available* but the new propoxyphene formulations are soluble in warm water and on a pharmacological basis can be utilized intravenously for the same effect.

8. Single doses of dextropropoxyphene in excess of 800 mg can be lethal if untreated and it is estimated that in excess of 200 individuals die yearly of dextropropoxyphene overdose in the United States.

9. Most abusers of dextropropoxyphene appear to obtain the drug by legal prescription but thefts of Darvon from pharmacies and practitioners are being reported and the drug is available on the street at $0.25-$1.50. per capsule.[27]

In summary, DPX's narcotic-like pharmacologic properties have made it a highly abuseable drug.

OLDER DPX DEATH STUDIES

In a huge Lilly-sponsored study involving medical examiners with a jurisdiction covering 52 million people, it was reported that DPX had been implicated in at least 1,022 deaths by the middle of 1975.[28] The authors found that, "the number of deaths involving propoxyphene is increasing each year, and at a faster rate than total drug deaths." They also found that "65.9% of all the cases had the word propoxyphene in the 'cause of death' statement on the death certificate." and that "in 34.1% of the cases the cause of death was officially attributed to something other than propoxyphene alone." In Detroit, the number of drug deaths involving DPX tripled from 1973 to 1975.[29] A similar pattern was observed in North Carolina, with 21 such deaths in 1973, 30 in 1974, and 16 during just the first three months of 1975.[30]

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* Although the easily separable DPX pellet is no longer found in Lilly DPX capsules, at least a few other pharmaceutical companies still produce DPX in this highly abuseable preparation. See FDC Reports, December 12, 1977.

The aforementioned study commissioned by the Justice Department provided an analysis of drug-associated fatalities reported in the DAWN system* from July 1973 to September 1975. This analysis showed that DPX was involved in 1,221 deaths, second only to heroin. Furthermore, DPX displayed the greatest relative toxicity of all the drugs reported in the DAWN system. One measure of toxicity utilized was deaths per 1000 emergency room mentions of the drug in the DAWN statistics as compiled in a Department of Justice study on DPX abuse.[31] Reports from coroner's offices of drug-related deaths divided by the number of mentions for the same drug in the DAWN emergency room network showed that DPX was the highest of any drug with 113 coroner-reported deaths for every 1000 emergency room mentions. It ranked ahead of heroin/morphine(98) diazepam (valium)(18) and phenobarbital (104).

Another index of its fatal toxicity as a function of how often it is prescribed can be found by dividing the number of deaths by the number of prescriptions for the drug. Again, DPX outranked all prescription drugs(including diazipam) in the same study.[32]

Why is DPX so toxic? As with other narcotics, it can cause pulmonary edema (fluid accumulation in the lungs) and respiratory depression which can frequently result in fatal respiratory arrest.[33-36] In addition, DPX and its metabolites can depress electrical conduction in heart muscles which can result in arrhythmias and cardiac arrest.**[37-48] Fatalities among those using the drug for its psychic effects are due to the small margin of safety between toxic doses and those required to achieve euphoria.[49,50]

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* Drug Abuse Warning Network, a Drug Enforcement Administration program then operating in 46 states. The statistics cover reports from hospital emergency rooms and from medical examiners (i.e. coroners), who had submitted reports at least 90% of possible reporting days during the life of the DAWN program.

** Specifically atrioventricular nodal conduction. The implication of this important finding is that persons with underlying cardiac disease who take DPX even at prescribed doses may inadvertently trigger an arrythmia culminating in cardiac arrest.

RECENT DPX DEATH DATA

From April 1975 to June 1977, DPX remained the second most commonly mentioned drug in DAWN coroners' reports after a combined category of heroin (Schedule I) and morphine (Schedule II).[51]

Most recently, as heroin has become somewhat better controlled--at least as reflected by a reduction in deaths from its use--DPX-related deaths have surpassed heroin(and morphine) related deaths in many cities. According to the latest DAWN report published by the Drug Enforcement Agency,[52] in 14 of the 23 cities (61%) for which data comparing DPX-associated deaths with heroin/morphine deaths were available, DPX was associated with more deaths than heroin/morphine in the first half of 1977.*

These cities were: BOSTON, BUFFALO, CLEVELAND, DALLAS, DENVER, INDIANAPOLIS, MIAMI, MINNEAPOLIS, NEW YORK, OKLAHOMA CITY, PHILADELPHIA, PHOENIX, SAN ANTONIO, SEATTLE.

The DAWN statistics also demonstrate that DPX has been abused much more frequently than several Schedule II drugs. The following table shows the number of mentions that DPX, methaqualone (Quaalude), amphetamines, and secobarbital received in the total DAWN system during the last full year for which comparative data were available.

TABLE I

PROPOXYPHENE(DPX) RELATED DEATHS
(JULY 1976 - JUNE 1977)
CORONERS' REPORTS

DRUG	# CORONERS' REPORTS	
Dextropropoxyphene(DPX)	491	
Diazepam(Valium)	388	
Meprobamate(Miltown)	316	SCHEDULE IV
Chlordiazepoxide(Librium)	70	
Flurazepam(Dalmane)	66	
Amphetamines	27	
Methaqualone(Quaaludes)	57	SCHEDULE II
Secobarbital(Seconal)	222	

Similarly, as also shown in the table, the DAWN statistics show that DPX is more frequently abused than the reported Schedule IV drugs.

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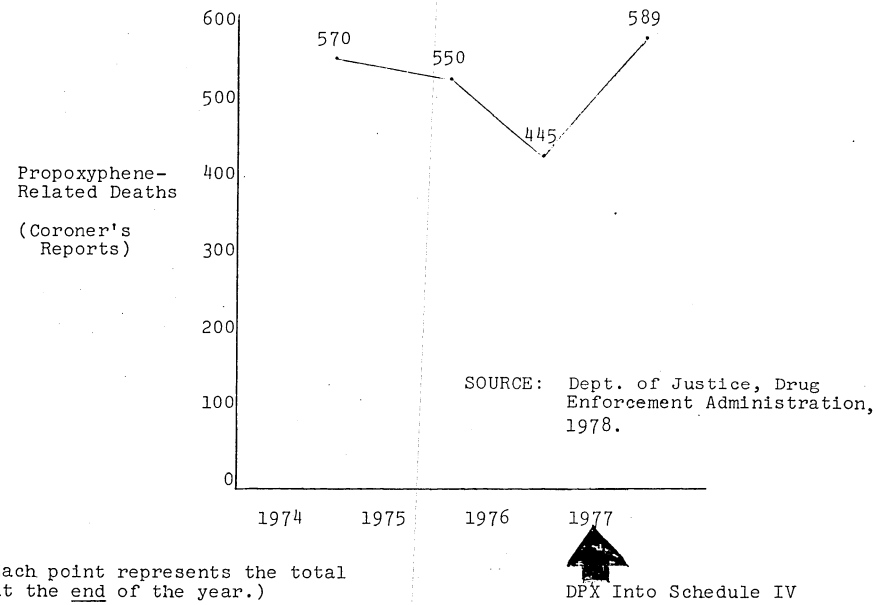
* The most recent time period for which data are available.

In relation to reported Schedule IV drugs, DPX is involved in more coroners' reports than the three others.

Although these comparative data include just 3 months during which DPX had become subject to Schedule IV restrictions, more recent data* including all of 1977 reveal that the control requirements of Schedule IV have failed to significantly alter the prevalence of DPX abuse. Figure 1A shows the time trend for the past four years for DPX-related deaths.

FIGURE 1A

TIME TREND FOR DPX-RELATED DEATHS



SOURCE: Dept. of Justice, Drug Enforcement Administration, 1978.

(Each point represents the total at the end of the year.)

It can be seen that deaths involving DPX declined somewhat between 1975 and 1976, due, perhaps in part, to the warnings then appearing in the medical and lay press.[53,54]

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* Obtained from the Section of Information Systems, Drug Enforcement Administration, Washington, DC.

However, by the time DPX was added to Schedule IV (March 1977), these drug-related deaths were once again on the increase. The total number of DPX-related deaths in the U.S. for the last 4 years is 2,154 Recent reports of DPX-related deaths from abroad indicate that this crescendo of abuse is not limited to the United States.[55-59]

DPX-RELATED-DEATHS

As mentioned previously, in about 2/3 of cases, DPX is mentioned on the death certificates as "cause of death" whereas in 1/3 of cases the death is attributed to "something other than DPX alone." [60]

In this Lilly-sponsored study[61] in 24% of the DPX-related deaths, DPX was the only drug involved and in an additional 18% DPX and alcohol were involved. In other cases, even though additional drugs were involved, DPX was mentioned on the death certificate in the"cause of death" statement.

More recent data show an increase in the percentage of cases in which DPX was the only drug involved. By 1977 (See Figure 1A) there were 589 DPX-related deaths of which 190 or 32% involved only DPX. (Up from 24% in the Lilly study and 23.8% in 1976.)

DPX DEATH RATES IN U.S. CITIES

In order to compare various U.S. metropolitan areas in terms of DPX-related deaths, the number of such deaths for each area between July 1973 and December 1977 was divided by population (in millions) of that area. These results can be seen in Table 2.

TABLE 2

PROPOXYPHENE(DPX-AS IN DARVON)DEATH RATES
FOR U.S. METROPOLITAN AREAS[a]

Rank	Area	DPX-Related Deaths (7/73-12/77)[b]	Population[d] (In Millions)	Deaths/Million People
1	Phoenix	81	1.218	66.5
2	San Francisco	189	3.129	60.4
3	San Diego	95[c]	1.588	59.8
4	Dallas	80	1.690	47.3
5	Denver	61	1.387	44.0
6	Los Angeles	276	6.945	39.7
7	Cleveland	78	1.975	39.5
8	San Antonio	37	.949	39.0
9	Miami	52	1.439	36.1
10	Buffalo	46	1.327	34.7
11	Detroit	132	4.174	31.6
12	Oklahoma City	21	.683	30.7
13	Philadelphia	133	4.797	27.7
14	Boston	72	2.731	26.4
15	New York City	274	11.316	24.2
16	Chicago	151	6.983	21.6
17	Atlanta	32	1.532	20.9
18	Washington, DC	60	2.936	20.4
19	Indianapolis	15	1.147	13.1
20	Minneapolis	20	1.846	10.8
21	Seattle	14	1.411	9.9
22	Kansas City	11	1.268	8.7
23	New Orleans	9	1.094	8.2

a. These are the 23 metropolitan areas which have been under surveillance by the DAWN Network for at least 2 1/2 years.

b. DPX-Related Deaths(except San Diego) are from Information Systems Section of Drug Enforcement Agency, Department of Justice. Included are all deaths where drug is a contributing factor or in which a toxic level is found (or suspected because of ingestion history).

c. Deaths for San Diego are from San Diego coroner's office since San Diego did not become part of the DAWN System until mid-1975. (San Diego includes only 1974-1977.)

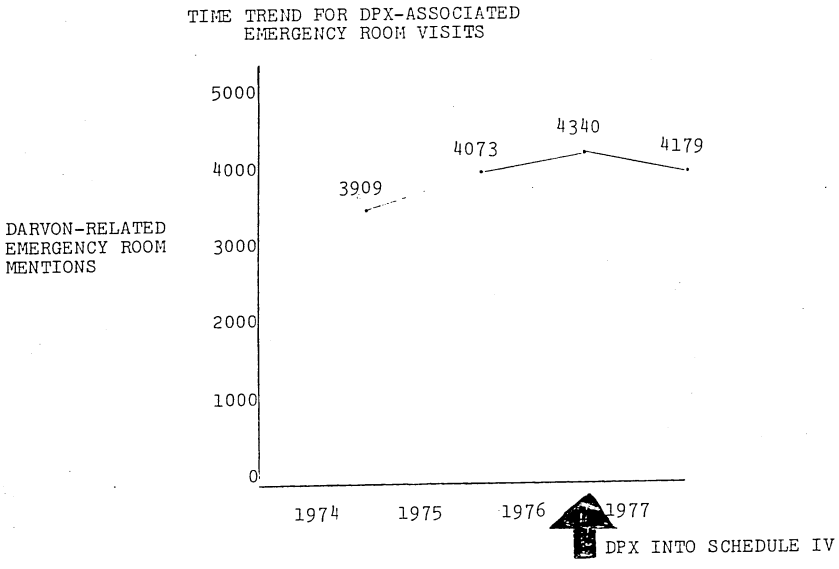
d. Populations of metropolitan areas are from DAWN (Department of Justice) Quarterly Report (July-September 1977).

For example, Phoenix, the leading U.S. metropolitan area--as far as DPX-associated death rates--had 81 deaths during that interval. With an area population of 1.218 million the rate was found to be 81 divided by 1.218 or 66.5 deaths per million.

At the other end of the list of metropolitan areas is New Orleans. Its DPX-death rate is 8.2 per million or less than 1/8 that of Phoenix.

Inspection of the time-trend of DAWN emergency room reports, as seen in Figure 1B, reveals that there has also been no remarkable decline since Schedule IV controls were imposed early in 1977.[62]

FIGURE 1B



(Each point represents the total at the end of the year.)

Clearly the controls of Schedule IV have not significantly diminished the reported abuse of this drug. Moreover, since the DAWN statistics only account for approximately 30% of U.S. population with 582 emergency rooms and 103 medical examiners (coroners)

included in the system, the above data, represent only a partial picture of DPX abuse.[63]

As can be seen in Table 3, within a year after amphetamines, methaqualone and secobarbital were placed in Schedule II, there were decreases of 50%, 52.4%, and 47.6% respectively, in the number of prescriptions. Within 4 years, all had decreased substantially more so that prescriptions for each were about 25% of what they had been before Schedule II was imposed. Placing drugs in Schedule IV, however, has much less effect on the number of prescriptions. For diazepam (valium) Schedule IV caused only a 6.9% decrease in prescriptions the first year.

TABLE 3

EFFECT ON THE NUMBER OF PRESCRIPTIONS OF PLACING DRUGS IN SCHEDULE IV OR SCHEDULE II

		Annual Number of Prescriptions (Millions)		
	Drug	Before Scheduling	1 Year After	% Change In Prescriptions
Schedule IV	Diazepam (Valium)	58 Million	54 Million	-6.9%
	Flurazepam (Dalmane)	11.5 Million	12.75 Million	+10.9%
	Propoxyphene (Darvon)	37 Million	33.5 Million	-9.5%
Schedule II	Amphetamines	16 Million	8 Million	-50.0%
	Methaqualone (Quaaludes)	42 Million	20 Million	-52.4%
	Secobarbital (Seconal	8 Million	4.3 Million	-47.6%

Flurazepam, already on the rise when placed in Schedule IV, rose an additional 10.9% during the first year.

Thus, placing DPX in Schedule IV has predictably had little effect on the number of prescriptions, availability or abuse(See Figure 1A, p 7, as measured by annual DPX-deaths). Since there is continuing evidence even relative to the Schedule II drugs for its abuse (See Table 1, p 6),DEA should transfer DPX to Schedule II.

VI. Criterion 2 - Accepted Medical Use

A second finding that must be made if a drug is to be included in Schedule II is that it have an "accepted" medical use or an accepted medical use with severe restrictions. 21 U.S.C. § 812(b)(2). Over thirty million prescriptions for DPX preparations were issued and refilled in 1977,[64] providing evidence that DPX is still widely "accepted" in the medical community, despite considerable evidence that at best DPX is no more effective an analgesic than aspirin.[65] Physicians' misconceptions about the effectiveness and the abuse potential of this drug have led to overprescribing and abuse.

Among patients whose source of drugs could be ascertained in DAWN emergency rooms, over 90% had obtained their DPX with legal prescriptions.[66] In a recent survey of physicians' attitues towards various drugs, DPX was rated as one of the most innocuous, while other controlled substances which are less lethal than DPX (e.g. Librium, Seconal, Methadrine and Phenobarbital), were considered to be more dangerous.[67] Thus the abundant prescribing of DPX could be more accurately characterized as an "accepted medical mis-use."

However, DPX Napsylate (DPX-Nap) does have a medical use in the detoxification and maintenance of narcotic addicts,[68-70] although the use of DPX for the purpose is presently under the Investigational New Drug Provision of the Food, Drug and Cosmetic Act. In high doses DPX-Nap exerts significant morphine-like effects, and can suppress symptoms of withdrawal from other narcotics.[71] The literature suggests that DPX-Nap may be most beneficial in assisting withdrawal from methadone.[72-73] DPX-Nap is physically less addictive than methadone, which has made it attractive as an agent to detoxify narcotics addicts. However, because such high doses are required to suppress symptoms of narcotic withdrawal and because DPX has such a high potential for abuse, detoxification must be carefully supervised and access to DPX-Nap strictly controlled.

Other than narcotic detoxification, not yet an "approved" indication for use of the drug, its use as a pain-killer or analgesic is clearly an accepted medical use even though, as discussed above, it has led to widespread abuse and, as will be seen, is much less effective than generally believed.

We would agree with the statement in the January 3, 1970 Medical Letter that "65 mg dose of DPX has mild analgesic effect and can be tried in patients in whom the usual doses of analgesics such as aspirin or acetaminophen (as in Tylenol or Datril) are not effective or not tolerated."

We would add, however, that the number of such people is extremely small and were the use of DPX limited to this population, the number of prescriptions would be more like 300,000 per year than 30 million (1/100 as much use as now).

VII. Criterion 3 - Dependence (Addiction)

The last finding that must be made regarding DPX is that its abuse may lead to severe psychological or physical dependence.* 21 U.S.C. § 812(b)(2)(c). This disjunctive language of the Controlled Substances Act indicates that a finding of either severe psychological or physical dependence resulting from DPX abuse will justify its inclusion in Schedule II. There is substantial evidence that DPX can produce strong psychological dependence and, sometimes, significant physical dependence.

Clinical trials have shown that DPX can produce physical addiction, as manifested by withdrawal symptoms. Although this apparently does not occur at recommended doses for relief of pain,[74] patients undergoing narcotic withdrawal using DPX-Nap have become physically addicted to the latter.[75] In 1956, Fraser and Isbell

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* As used herein, physical dependence refers to a condition of latent central nervous system hyperexcitability induced by frequent administration of a drug. Signs and symptoms of abstinence or withdrawal appear when drug administration suddenly ceases. (In the case of opiates, a withdrawal syndrome can be precipitated by administration of narcotic antagonists such as naloxone and nalorphine.) Psychological dependence on a drug can develop along with, or in the absence of, physical dependence. A salient characteristic of psychological dependence on a drug is the tendency for the latter to provide positive reinforcement for repetitive drug use by direct action on the central nervous system.

concluded that:

> "[D-propoxyphene] has addictive liability. This is indicated by, (a) the induction of opiate-like symptoms when administered in large oral doses to former opiate-addicts, (b) its ability to partially suppress signs of abstinence from morphine, (c) the production of consistent, although very mild, signs of abstinence when the drug was abruptly discontinued after 53 or 54 days of addiction in five subjects."[76]

Four years later these investigators undertook controlled experiments which suggested that the addictive potential of DPX was "substantially less than that of codeine."[77]

Case reports tend to substantiate the claim that the physical dependence produced by DPX is generally moderate; however, psychological dependence can be significant. Elson and Domino reported a case of DPX addiction "characterized by extreme psychic craving, euphoria, and tolerance to the dextropropoxyphene hydrochloride...The patient showed definite withdrawal signs, including chills, profuse perspiration, cramping, abdominal pain, headaches, nervousness and diarrhea."[78] (emphasis added)

Reviewing the literature on DPX dependence in 1971 (six published reports), Salter stated:

> "It is evident from these reports that propoxyphene can produce both strong psychological dependence and some degree of physical dependence, although quantitatively, less than that of morphine or codeine. Significant tolerance does occur and mild to moderate withdrawal symptoms may sometimes be elicited in a dependent person by sudden discontinuance of the propoxyphene."[79] (emphasis added)

Occasionally physical withdrawal symptoms may be severe. Mattson et al. described 4 patients chronically dependent on high doses of DPX:

> "Not only did the patients continue using the drug for its psychic effect, but 3 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."[80]

Judging from the published literature, oral abuse usually appears to lead to dependence and psychic craving only in doses much higher than the so-called therapeutic dose for relief of pain symptoms.[81] Yet Salguero et al. described a case of severe psychic (but minimal physical) dependence in an individual whose average intake was only 65 mg every 2 to 4 hours, or just 1.5 to 3 times the recommended therapeutic dose.[82] The Justice Department study even noted cases of psychic dependence developing at the recommended therapeutic levels for pain.[83]

Addiction to DPX may occur in individuals with no prior psychiatric history or drug abuse. Exemplifying DPX addiction in persons innocent of prior drug abuse are cases of newborn infants, addicted in utero, who have displayed signs and symptoms of withdrawal shortly after birth.[84,85,86] In 1974, in a review of the literature and presentation of seven new cases, Maletsky provided convincing evidence that:

1. Addiction to propoxyphene can occur in individuals neither psychiatrically ill nor "addiction prone";
2. Addiction can occur under the usual circumstances of medical prescribing;
3. Tolerance and withdrawal can be clearly demonstrated;
4. Addiction can occur without the initial euphoria.[87]

(emphasis added)

Considering the relative analgesic ineffectiveness of DPX at low doses, it is not difficult to understand why patients might increase their dosage in trying to achieve better pain relief, however, some patients may become inadvertently addicted.

It is clear that oral administration is sufficient to maintain addiction; intravenous injection is not necessary.[88] Indeed, dependence cannot be maintained for long by intravenous or subcutaneous infusion because of DPX's destructive effects on the veins and soft tissues.[89] Nevertheless, narcotic addicts shoot DPX intravenously when more potent narcotics are in short supply, e.g., when the addicts are incarcerated.[90]

In light of the foregoing evidence of psychic and physical dependence and tolerance, the Administrator of the DEA found that "Abuse of DPX may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III."[91] If this is true, the dependence produced by drugs and other substances in Schedule III, and a fortiori by those in Schedule II, should be considerably more severe. Yet it is not clear that certain drugs in Schedule II produce any greater degree of physical or psychologic dependence than DPX. Of amphetamines, for example, a widely-used medical textbook states that, "Physical dependence manifested as withdrawal signs is difficult to establish...The development of tolerance is also not easy to prove."[92] Goodman and Gilman, an authoritative pharmacology text states:

> For a long time it was believed that, except for drug craving, prolonged sleep, general fatigue, lassitude, and depression, there were no withdrawal symptoms from amphetamine-like drugs and, therefore, no physical dependence...It is still considered true that abrupt discontinuation of sympathomimetic amines does not cause major, grossly observable, physiological disruptions that would necessitate the gradual withdrawal of the drug. But the prolonged sleep, lassitude, fatigue, and depression, that follow discontinuation of these drugs are difficult to attribute merely to the preceding loss of sleep and weight...Most observers now recognize the existence of a withdrawal syndrome following discontinuation of amphetamine-like drugs. Its role in perpetuating drug use or relapse is not clear.[93] (emphasis added)

The relation between this withdrawal syndrome, characterized by fatigue and hunger, and amphetamine use has not even been firmly established. Yet amphetamines have been included in Schedule II, despite the lack of evidence of severe physical dependence.

DPX is far more widely abused than the amphetamines and, when abused it produces a comparable degree of psychological dependence and a greater degree of physical dependence. Thus DPX represents an even stronger case for inclusion in Schedule II.

VII. Analgesic Impotence of Propoxyphene

While DPX's potential for abuse has been understated, the claims for its analgesic potency have been grossly exaggerated. No significant analgesic effect has ever been shown for DPX preparations in properly conducted* clinical studies. In a review of the published literature undertaken in 1970, Miller et al., discovered that only 20 of 243 "studies" on DPX had been conducted double-blind.**[94] Even among these 20 studies, several had design defects such that their results were of questionable validity. Gleaning what remained of the analgesic efficacy of DPX in relieving several kinds of pain, the authors concluded: "Propoxyphene is no more effective than aspirin or codeine and may even be inferior to these analgesics...When aspirin does not provide adequate analgesia, it is unlikely that propoxyphene will do so."

Sixteen of the studies reviewed by Miller had compared DPX with placebo. In nearly half of these(7/16), there was no significant difference in analgesia between DPX and placebo. Four of these latter studies included tests using 65 milligram (mg) doses of DPX, which remains the manufacturers' suggested dose.[95]

Three more recent double-blind studies have suggested that, at the manufacturer's recommended dose, DPX is no more effective in pain relief than placebo.[96,97,98] Moertal et al. concluded:

> "The therapeutic credentials of both propoxyphene(Darvon) $9.50 per 100 doses of 65 mg) and ethoheptazine(Zactome, $7.40 per 100 doses of 75 mg) must be classified as very equivocal. In this study, neither showed a significant advantage over placebo, and both were significantly inferior to aspirin."[99]

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* I.e., including,at a minimum, randomization and double-blind observation.

** A double-blind trial exists where neither patient nor observer knows which treatment the patient is receiving. This minimizes bias and preconceptions of patient and observer both, and is imperative in a study design in order to achieve meaningful results.

Although Dr. C.M. Gruber, one of Eli Lilly's medical spokesman, took exception to this conclusion,[100] his own published investigations have also shown that DPX is no more effective than placebo in single 65 mg doses.* [101]

In 1977 Miller reviewed 13 double blind studies** of DPX's analgesic effectiveness, twelve of which had been published subsequent to his earler review.[102] Five of these thirteen studies purported to evaluate the relative efficacy of DPX hydrochloride and DPX napsylate, which was introduced in 1971 by the Lilly Company just before its patent on DPX hydrochloride expired. Miller's conclusion: "The introduction of the napsylate salt PRX [i.e. dextropropoxyphene] has not provided a more effective preparation, and the napsylate has no other clinically significant advantages over the hydrochloride."

Lacking proof of superior analgesic efficacy, the popularity of DPX Napsylate products (Darvon-N, Darvocet-N, Darvon-N with ASA, etc.) attests to the superior efficacy of the Lilly Company's promotional efforts.

The other eight studies reviewed by Miller once again failed to demonstrate that DPX had any analgesic advantage over the other less expensive medications. Indeed, as noted above, three of these studies suggested that DPX was no more effective than placebo.

Miller's review also discussed all the double-blind studies comparing DPX hydrochloride and DPX napsylate combination products with other analgesics. Considering the paucity of well-designed studies comparing combination drugs with single analgesics, the fact that most analgesic preparations prescribed are combinations is surprising. Miller found only one well-designed study comparing acetaminophen (the active ingredient in Tylenol, Datril, etc.), acetaminophen plus DPX (i.e. Darvocet), DPX alone, and placebo.[103]

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* Dr. Gruber's conclusion in his 1977 study (note 90) that DPX in multiple doses does provide significantly greater relief than placebo is suspect because he neglected to randomize the patients in his study.

** Including 2 of the 3 just discussed.

That study demonstrated that acetaminophen alone was as effective in pain relief as acetaminophen plus DPX. In other words, the analgesic property of this combination can be attributed to the acetaminophen by itself.

Similarly, in his review Miller discovered only one good study comparing aspirin with aspirin plus DPX.[104] The authors of that study found that propoxyphene napsylate plus aspirin was "significantly inferior to aspirin plus either codeine or oxycodon; but not significantly different from aspirin alone." In other words, here once again, the DPX combination analgesic provided no significant benefit over plain aspirin.

Finally, of only five double-blind studies on DPX and aspirin, phenacetin, and caffeine (APC) combinations, Miller found that two compared DPX and APC with APC alone. One of these two studies found that DPX Napsylate plus APC was superior to APC alone.[105] This alleged superiority of DPX-APC over APC alone must be interpreted in light of the above-mentioned well-designed studies where no such difference in pain relief attributable to DPX could be detected. That is, the alleged advantage of DPX plus other analgesics must be quantitatively minute since none but this particular Lilly study could discover it.

Thus Miller states: "There is little evidence that combinations of PRX[i.e. DPX] with other analgesics are superior to one analgesic alone. Aspirin or acetaminophen appears to be just as effective when given alone as when given with PRX."

In conclusion he declares:

> "It is now more doubtful than ever that PRX HCl[i.e. DPX] 65 mg provides an analgesic effect equal to that of aspirin 650 mg...There is no conclusive evidence that combinations of PRX with other analgesics are more effective than PRX or other analgesics alone. In view of these findings, the continued widespread use of PRX preparations is perplexing."

It is clear that from a therapeutic standpoint, little if anything would be lost by restricting the availability of DPX. DPX is apparently no more effective in pain relief than aspirin or acetaminophen.

IX. Legal Analysis

The evidence of the actual abuse and acute toxicity of DPX summarized above demonstrates that the more stringent Schedule II controls are now warranted. DPX's abuse potential has been compared to that of other drugs which have been placed in Schedule I by DEA. As Dr. Theodore Cooper, then Assistant Secretary for Health admonished in a 1976 memorandum recommending that DPX be placed in Schedule IV:*

> "As with most psychoactive drugs, abuse potential of a particular drug is usually described in terms of prototype or 'reference' drugs. In this respect, propoxyphene has been compared to codeine, morphine and heroin. Such comparisons have included both acute physiological and psychological effects of propoxyphene and the chronic effects of high dose administration."[106]

Dr. Cooper acknowledges DPX's potential for abuse and acute toxicity are well recognized, and the facts of widespread actual abuse confirms Dr. Cooper's reference to the similarities between DPX and heroin and morphine. Perhaps most compelling of the evidence thus far assembled concerning the extent of DPX's actual abuse is the DAWN statistics which demonstrate that deaths involving DPX abuse in 14 major metropolitan areas occur more frequently than deaths involving heroin and morphine combined.[107]

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* Although Dr. Cooper recommended that DPX be placed in Schedule IV, it's difficult to reconcile this recommendation with his finding that DPX's potential for abuse is equivalent to substances like heroin and morphine, which have been placed in Schedule I. However, whatever reasons Dr. Cooper may have had in 1976 for not advocating more stringent controls on DPX, his recommendation was untenable in light of then existing statistics which established the unchecked actual abuse of DPX.

The effect of transferring DPX to Schedule II is that the drug will be subject to requirements that prescriptions be in writing and may not be refilled, 21 U.S.C. § 829(a), and that the drug will not be produced in excess of government-established quotas based on estimated medical and scientific need. 21 U.S.C. § 826(c). In contrast, Schedule IV allows prescriptions for DPX to be transmitted orally and refilled five times in any six month period. 21 U.S.C. § 829(b). Moreover, the penalty for violating provisions of the Act where a Schedule II drug is involved is substantially more severe than for a Schedule IV drug.[108] As has been the case with amphetamines and other widely abused drugs which DEA has been forced to transfer into Schedule II to curb their abuse, DPX abuse will not subside unless the more stringent Schedule II controls are imposed.

Because of the CSA's overriding emphasis on protecting the public from hazardous drugs, Congress, in the CSA Act, requires the Attorney General to determine the schedule in which to place a particular drug on the basis of three factors; its potential for abuse, its currently accepted medical use, and the degree to which it causes physical or psychological dependence.[109] To provide guidance to the Attorney General, the statute further states that the Attorney General's inquiry must include an evaluation of the following factors:

1. Its actual or relative potential for abuse.
2. Scientific evidence of its pharmacological effect, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current pattern of abuse.
5. The scope, duration and significance of abuse.
6. What, if any, risk there is to the public health.
7. Its psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled under this subchapter. [21 U.S.C. § 811(c).]

In addition to the factors listed in Section 811(c) of the Act, the Attorney General must request the recommendation of the Secretary of HEW, including the Secretary's consideration of the eight factors listed above. 21 U.S.C. § 811(b).

It is apparent from the statute that the critical inquiry in considering whether to transfer a substance to a more stringent category is its potential for abuse. Indeed, the statute requires that this factor be considered before any further proceedings are initiated. 21 U.S.C. § 811(a)(1)(A). Furthermore, four of the criteria enumerated above specifically concern the substance's potential for abuse. 21 U.S.C. §§ 811(1),(4),(5) and (6).

The statutory emphasis on the substance's potential for abuse and the Congressional intent that abuse be the principal, if not the determinative part of the inquiry is confirmed by the House Report accompanying the passage of the Act, which describes the factors influencing the Attorney General's inquiry as follows:

> A key criterion for controlling a substance, and the one which will be used most often, is the substance's potential for abuse. If the Attorney General determines that the data gathered and the evaluations and recommendations of the Secretary constitute substantial evidence of potential for abuse, he may initiate control proceedings under this section. Final control by the Attorney General will also be based on his findings as to the substance's potential for abuse.[110]

The House Report continues with the definition of "potential for abuse", which includes factors relating to (1) the health of the drug user or the safety of the community; or (2) the extent that the drug is diverted from legitimate drug channels; or (3) the finding that individuals are taking the drugs on their own initiative rather than on the basis of medical advice.[111] Unquestionably, the hundreds of deaths due to DPX overdose each year illustrate that DPX's potential for abuse exceeds the requirements of each of these criteria.

In a similar vein, the House Report further provides that "misuse of a drug in suicides and attempted suicides, as well as injuries resulting from unsupervised use are regarded as indicative

of a drug's potential for abuse.[112] In this context, it is significant that 55% of the emergency reeom mentions of DPX from July-September 1977 consisted of suicide attempts, according to the DAWN statistics.[113] Another 18% were associated with addiction or "psychic effects."[114]

Furthermore, the courts which have construed the CSA have also relied almost exclusively on the substance's potential for abuse in reviewing the propriety of decisions to place a drug in a particular schedule. Indeed, in The National Organization for the Reform of Marijuana Laws (NORML) v. Drug Enforcement Administration, 559 F.2d 735(D.C.Cir. 1977), the Court of Appeals rejected DEA's claim that the lack of established medical use for cannabis, standing alone, required that it be included in Schedule I. 559 F.2d at 747. Rather the Court held that under the CSA, DEA is bound to balance medical usefulness against the other factors enumerated in the Act, which the Court summarized as the potential for abuse and the danger of dependence. cf. United States v Maiden, 355 F.Supp. 743, 748-749 n.4 (D.Conn. 1973)

In addition to evidence of DPX's overwhelming abuse, two other factors further point to the need for tighter controls on DPX's availability. First, DPX's toxicity, discussed above.[115] DPX is particularly dangerous because the margin between the doses necessary to achieve the euphoric state and those which are harmful and often lethal is extremely narrow. As DEA recognizes, although the statute and the legislative history are silent on the weight to be given to acute toxicity in assessing the appropriate schedule for a substance, toxicity is an extremely important consideration to weigh.[116] In the case of DPX, toxicity weighs heavily towards the imposition of more stringent controls.

Second, the minimal therapeutic value of DPX must also be balanced against the harm and death that this drug is causing to hundreds of individuals each year. As demonstrated above, aspirin or acetaminophen(Tylenol) appears to be at least as effective when given alone as when given with DPX.[117] For those who can not take aspirin, and choose to take DPX over the other analgesics, Schedule II controls will hardly present a barrier to use of DPX, which will remain available on a prescription basis.

In conclusion, the extent of DPX abuse as presented above, plainly demonstrates that the present controls are wholly inadequate. DEA is required by law to curb the abuse of this minimally effective and extremely toxic drug by transferring DPX to Schedule II and should not retreat from its legislative mandate.

FOOTNOTES

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28. Finkle, B.S., et al., supra note 23.

29. Monforte, J.R., and W.U. Spitz, supra note 26.

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104. Moertel, C.G., et al., "Relief of Pain by Oral Medications, a Controlled Evaluation of Analgesic Combinations," JAMA 229: 55, 1974.

105. Bauer, R.O., et al., "Evaluation of Propoxyphene Napsylate Compound in Postpartem Uterine Cramping," J Med 5: 317, 1974.

106. Memorandum from Theodore Cooper, M.D. to Peter Bensinger, "Scheduling Recommendations for Propoxyphene," August 12, 1976.

107. See infra at 6.

108. The penalty under the Act where a controlled substance under Schedule II is involved is up to 5 years imprisonment, a fine of up to $15,000 or both. In the case of a Schedule IV Substance, the penalty is up to 3 years imprisonment, a fine of up to $10,000 or both. 21 U.S.C. § 841(b)(1)(B) and (b)(2).

109. 21 U.S.C. § 812. The findings required for Schedules II and IV are as follows:

(2) Schedule II
- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- (C) Abuse of the drug or other substance may lead to severe psychological or physical dependence.

(4) Schedule IV

- (A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.

- (B) The drug or other substance has a currently accepted medical use in treatment in the United States.

- (C) Abuse of this drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

110. H.R. 91-1444, 91st Congress, 2d Session pt. 7, at 34, cited in U.S. Code Cong and Admin New 1970, p 4601.[Herinafter referred to as H.R. 91-1444]

111. The term "potential for abuse"is adopted from Section 20 1(v) of the Food, Drug and Cosmetic Act as defined in 21 C.F.R. 166.2(e), cited in U.S. Code Cong. and Admin. News 1970, p 4601.

112. H.R. 91-1444, supra note 110, at 4602.

113. DAWN Quarterly Report, supra note 9,at 13.

114. Id.

115. Infra at 5.

116. Drug Enforcement, Vol 2, No 2, Spring 1975, at 39.

117. Infra at 17.

Senator HAYAKAWA. Mr. Chairman, I am called to Foreign Relations to fill out a quorum, but I do want to ask a question.

Senator NELSON. Go ahead.

Senator HAYAKAWA. When you say, Dr. Wolfe, that Darvon is less effective than aspirin, is it not true that, depending on the individual, for some people Darvon is more effective and for some people it is not, that people go from one to the other as a painkiller, because of the unique differences in each of us, as individual physiological systems?

Dr. WOLFE. Well, that is an interesting question.

Pain is a very difficult thing to measure, and in some studies, there are a number of studies showing that giving a sugar pill, just a placebo, because of the doctor-patient intervention, will and can have a substantial relief on pain in someone. Therefore, when one does studies on large numbers of people, this has to be taken into account, so that not only does one want to compare Darvon or propoxyphene with aspirin, but also with a placebo. Whereas in individual cases, there may be someone who says they get a better response, overall when one accounts for the placebo effect and other problems, by means of properly controlled studies where patients have been randomized, and where investigators do not know whether a placebo or the drug has been given out, these studies really fail to show that propoxyphene or Darvon is any better than aspirin, and in many of them they show it is not as good as aspirin.

Senator HAYAKAWA. But these studies covering a large number of people still do not face the question of the individual.

If I as an individual find that aspirin does not work for me for a particular kind of pain, recurrent pain, and I find that Darvon does, does it matter what research on it of a few thousand people displays?

Dr. WOLFE. Yes and no.

In one sense if aspirin does not work, and there are some people who have intolerance to aspirin, they have an ulcer, whatever, another alternative is acetaminophen.

If that does not work, another alternative is codeine.

All three of these, as I will discuss shortly, are considerably safer than Darvon, and whereas there may be someone such as yourself who cannot take aspirin, we are not able to locate a group of people at all who find that aspirin, or acetaminophen, or codeine do not work.

There are three choices, not just one, other than Darvon.

Senator HAYAKAWA. These questions bother me; that is, there are many, many painkillers besides the two mentioned

Dr. WOLFE. And they are all safer, that is the main point.

Senator HAYAKAWA. That is not the question.

If people continue to take however more than the recommended dose, thereby endangering our health, as you say, is this the fault of the manufacturer, or is it the fault of the individual for failing to observe the recommendation.

If the prescription says recommended dose, not more than one every 4 hours, and people continue to persist in taking two or three or four every 2 hours, whose problem is that, is it the Government's problem?

I am asking you, does the Government have to be the universal babysitter, or is the Government to let people who are capable to decide for themselves whether or not to follow a recommendation given on a scientific basis.

Dr. WOLFE. Well, that is certainly a problem, whether we are talking about smoking or saccharin or Darvon, but I think in this case, because the drug is often not very effective, without being a drug abuser or a dope addict, whatever, many people may well understandably be inclined, having paid their money for the Darvon, to try two instead of one.

The thing that distinguishes this case from a lot of other drugs, is that you can start getting into trouble at very little more than the recommended dose.

There are other drugs, such as aspirin, where you have to take maybe 20 or 30 times above the recommended dose to start getting into serious trouble.

The margin of error, or the safety margin, is extremely low with Darvon, and as the San Francisco coroner in your home State has said, if you double the Darvon doses, and you take one or two bar drinks, you can get into the toxicological range.

The patient with cancer was under medical supervision, taking two instead of one every 4 hours.

This can happen. I think if Darvon were much safer than it is and more effective than it is, we could tolerate it.

There are a lot of drugs on the market where people can get into difficulty, taking 5, 10, 20 times the recommended dose, but you cannot put everyone in a glass house. In the case of Darvon, I think the drug needs to be put in a glass house, because it is so dangerous at low levels, probably, in many cases; because the metabolite is building up.

Senator HAYAKAWA. Thank you, Dr. Wolfe.

Excuse me, Mr. Chairman. I have to go to my other committee.

Senator NELSON. When you first responded to Senator Hayakawa's question, I think you said you made reference to something being safer than aspirin, and I think you meant safer than Darvon.

You better look at your testimony when you get the record back.

One further followup question on the point raised by Senator Hayakawa. The marketing of drugs is based upon a very specific statute, which says you must prove efficacy and safety by well-controlled scientific studies, and that does not permit subjective judgments by a physician and patient about what helps them or does not help them, since it has to be based upon well-controlled studies, as everybody knows.

Almost all problems people have are self-limiting. People all over this country—a substantial percentage of people—are getting from their doctor an antibiotic for a common cold, and there is not an antibiotic that affects the cold, because there are some 200 cold viruses. Yet they will get well, because everybody gets well, so they attribute the act of getting well to having taken an antibiotic, as having an effect on the virus causing the cold. That is why the statute has to be well-defined.

Dr. WOLFE. Another example that comes to mind, where both doctors and patients may have been inclined to say, I want to use this drug, because it seems to work, is where a properly controlled study was done to see whether the drug really worked is DES, also manufactured by the Eli Lilly Co. This drug was given to millions of women, and when a properly controlled study was done to see whether it really protected against miscarriages, it turned out it did not work at all.

In fact, in one study, it caused more miscarriages than the placebo, so that the fact an individual doctor might prescribe the drug does not mean it works.

What the study showed is that a woman who had a miscarriage in a previous pregnancy and who got the drug might have had a miscarriage anyway, even if she had not gotten the drug.

That points out what you are saying; we need to have well-designed, well-controlled studies, whether it is on the effectiveness of DES to prevent miscarriages to see that when a drug is first marketed it is effective.

Once the effectiveness law was passed, Darvon was reviewed, and certainly there were some questions raised about its effectiveness, particularly studies which showed that the drug was more effective than a placebo, but less effective than aspirin. That, in and of itself, would be grounds for marketing it, on the question of effectiveness alone.

I think here we have a double problem, not only is it less effective, or no more effective than a number of other painkillers, it also is considerably more dangerous.

Since we have been discussing the comparisons between Darvon and other painkillers, I have a chart on table IV, which examines the total number of deaths as measured by the drug abuse warning network system.

[The information follows:]

Drug	Deaths, 1977 [1]	Deaths per million prescriptions [2]
Darvon	590	19
Codeine	255	5
Aspirin [3]	150	<1
Acetaminophen [3]	77	<1

[1] DAWN Quarterly Report January–March 1978.
[2] 1977 prescriptions filled from National Prescription Audit, I.M.S.
[3] 1977 retail sales of aspirin of $500,000,000 and acetaminophen, $150,000,000—assume average cost of $1 for aspirin, $1.50 for acetaminophen and use deaths per million bottles.

Dr. WOLFE. In 1977 for Darvon and codeine, if you divide the total deaths by the number of prescriptions for aspirin and acetaminophen, all we were able to obtain were marketing figures for aspirin, retail sales, so for these two, we were able to figure out how many deaths per bottle sold there were, one index of aspirin and acetaminophen toxicity. For Darvon, there were 590 deaths during that reported period as listed in the Drug Abuse Warning Network Quarterly Report, January of 1978, and the rate of deaths per million prescriptions was 19.

Codeine was 255 deaths, or 5 deaths per million prescriptions.

Aspirin was 150 deaths, less than one per 1 million bottles, and for acetaminophen, it was 77 deaths, or also less than one death per million bottles sold—the same as for aspirin.

I note in looking at the Justice Department's testimony, that they point out that barbiturates, at least several of them, have a higher rate of deaths per million prescriptions.

An earlier report they put out in 1976, at least looked at one barbiturate, and they looked at the death and in that case the death rate was lower than for propoxyphene. In today's testimony they show the death rate per million prescriptions of barbiturates such as

Seconol. The importance of this is that recognizing the dangers of Seconol and most of the other barbiturates, the Justice Department has scheduled them in schedule II, and that has resulted in a substantial decrease in the prescribing of the drugs, in the emergency room visits occasioned by the use of the drug, and a lesser but important decrease in the deaths due to some of these drugs. In comparing something like Darvon to something such as Seconol in schedule II, it really points out that schedule II is able to have an important impact by decreasing prescribing of the drug.

Senator NELSON. Did you have handy, or did you put in your petition, I do not recall it, what happened in the prescription of amphetamines, when they were put on schedule II?

Dr. WOLFE. This is in the original petition.

On page 14 of the DEA (Department of Justice) petition, we looked at amphetamines, Quaalude and Seconol, and some others, to see what happened within 1 year of their being put into schedule II.

They experienced a 50 percent, 52 percent, and 47.6 percent fall in prescriptions, respectively, and by the end of 3 years, there was a decrease of approximately 75 percent.

In other words, only about a quarter or less of the prescriptions that had been written before scheduling, were written within several years afterward, so that at least as one of the alternative proposals that we have made to the Justice Department, or the HEW for controlling the drug, moving Darvon into schedule II would cause a major decrease in prescribing, and, therefore, in emergency room visits and deaths.

All of these have gone down somewhat since they have been put on schedule II.

Senator NELSON. Let me ask a question. On page 8 of your petition, you make reference to some 1,200 deaths reported by the Drug Abuse Warning Network from July 1973, to September 1975.

Dr. WOLFE. That was a study commissioned by the Justice Department. It is page 8 of the testimony.

Senator NELSON. I am puzzled about this 26-month period. Was that a selection of that period by you, or was that the study period done by Justice?

Dr. WOLFE. You are talking about page 6 of the petition to the Justice Department?

Senator NELSON. Yes.

Dr. WOLFE. There was a study commissioned by the Justice Department looking at those drugs associated with fatalities in parts of the country, about a third of the country, related to Darvon. This is their study, not ours.

Senator NELSON. That is the 26-month period they select themselves?

Dr. WOLFE. Yes.

Senator NELSON. Do not the statistics now indicate a reduction in the deaths from use of propoxyphene, if you take it by the quarter in 1978?

Dr. WOLFE. Well, not really.

On the bottom of page 4 of the testimony today, I go into that.

Let me just read these two sentences, and then answer your question as to why it appears that there may have been a decrease.

In the year before Darvon was put in schedule IV, March 1976 to February 1977, there were 459 deaths related to its use.

In the first year of schedule IV, March 1977 through February 1978, the number was 510.

Although there appears to be a decrease in deaths during the latter part of 1978, these data underestimate the eventual numbers of reported deaths, since all 1978 reports are not completed and sent to DEA until well in 1979.

In other words, if we look now, early 1979 or late 1978, or a year ago, early in 1978, if we looked at the last part of 1977, we would see what appeared to be a fall-off in deaths, not only due to Darvon, but anything else, simply because in terms of getting all these coroners' reports, it takes well into 1979, before they are complete. So that each year, if you look in January, it looks like everything is getting better, not only for Darvon, but for everything else.

If you look later in that year, there have been many more reports filed, so that at this time, all we can look at is the period up to the early part of 1978, where the data is complete, and that period of time, that 1 year after as opposed to the 1 year before, putting into schedule IV, really does not suggest any change.

There has been a fall in the emergency room visits, which I see the Justice Department will discuss in their testimony, but this has not, at least as of yet, been accompanied by any evidence of decrease of fatalities.

The prescribing has gone down from I think 33 million to 30 million over the last year or so.

It still is very widely prescribed.

Does that answer your question?

Senator NELSON. Yes.

Dr. WOLFE. As stated in the petition to HEW rescheduling Darvon in schedule II only makes sense if it is possible to identify a group of people for whom the substantial risks of the drug are outweighed by the questionable benefits, taking into account the availability of aspirin, codeine, and acetaminophen, all safer and more effective.

I am still unable to identify such a group of people and therefore believe an imminent hazard ban is the preferable way of meeting this serious problem.

Senator NELSON. Let me go back to that previous question.

Are you saying that DEA releases the statistics from the last quarter of 1978, which are not complete, and subsequent to that when all of the records are in, some time during the following year, they update that last quarter?

Dr. WOLFE. Yes; I think they have been very cautious about that.

Senator NELSON. Is that what happens?

Dr. WOLFE. That is what happens. They release on a fairly regular basis all of this data, but they point out, particularly for the last few months, that the data with respect to deaths is often understated, because they have not gotten all of the reports in yet.

Senator NELSON. As you say, if you look at any year in the past several years, it is the same pattern?

Dr. WOLFE. Yes.

Senator NELSON. Because Lilly has a chart that indicates a rather dramatic lowering.

Dr. WOLFE. I would say the chart is misleading, because each year it takes well into the following year before all of the reports are in, and this is nothing new, the Justice Department is perfectly aware of that.

Senator NELSON. Then what does DEA do in a succeeding year—with additional statistics as they come out? Do they update the last quarter of the previous year?

Dr. WOLFE. That is correct.

Senator NELSON. When they issue these statistics for the last quarter of the previous year, do they have a footnote saying these are incomplete?

Dr. WOLFE. Yes; they do.

Senator NELSON. So that shows in their footnote on the use of Darvon for the last quarter of 1978?

Dr. WOLFE. Yes.

Again, I just had a glance at it a few minutes ago, I think in their statement this morning, they point out the reports, not only for the last quarter, but perhaps for the last half of the year of 1978, are not complete yet, and, therefore, even though it appears the number of deaths are falling, that may not eventually turn out to be the case, so they do point that out in their testimony this morning.

Senator NELSON. OK.

Dr. WOLFE. One other thing, when the possibility of putting Darvon in a different schedule (schedule IV) was raised in 1973, Lilly responded and I quote, "we believe it would not have any material effect on the sale of the product."

I think they anticipated that schedule IV, which certainly is nowhere near as strong as schedule II, often does not have a substantial effect on prescribing.

In our petition to the Justice Department, we looked at two other drugs that had been placed in schedule IV, Valium and Dalmane, and in each case, there was very little effect in the first year, after placing them in schedule IV.

Valium went down 4 percent, and Dalmane, which was on the rise, continued to rise, so schedule IV is not anywhere near as effective as schedule II, in terms of controlling use and the predictable consequences of people using a drug as dangerous as Darvon.

As stated in the petition to HEW, rescheduling Darvon in schedule II only makes sense if it is possible to identify a group of people for whom the substantial risks of the drug are outweighed by the questionable benefits, taking into account the availability of aspirin, codeine, and acetaminophen, all safer and more effective.

I am still unable to identify such a group of people and therefore believe an imminent hazard ban is the preferable way of meeting this serious problem, This is the problem Senator Hayakawa raised, someone who cannot take aspirin or codeine or acetaminophen. When you look at all three, I would like to see what people would not benefit from at least one of those.

Senator NELSON. You are saying there is no target group for whom Darvon would be a better drug than either codeine, acetaminophen, or aspirin?

Dr. WOLFE. That is correct, all of which are much less expensive and much less dangerous as I pointed out.

I have never seen any evidence of that at all, and I think that is a critical issue.

In a letter to me from Dr. Quentin Young, chief of medicine at Cook County Hospital in Chicago, dated January 23, 1979, he states that Darvon was banned from the medical clinics there in 1974 and from the entire hospital in June 1977.

This is the second largest medical clinic in the United States.

Dr. Young said:

The reasons for eliminating Darvon from the drug list included high cost and absence of any therapeutic superiority over aspirin and aspirin-related drugs for its legitimate indications. Another, more serious concern was our observation, in this large public hospital, that Darvon was increasingly utilized as an illicit drug by persons who had become dependent upon it.

We concluded that an agent devoid of any significant, unique value which was the object of dangerous abuse by growing numbers of people, had no place on our hospital outpatient formulary.

While I feel that we served our patients well by avoiding this potentially dangerous drug, we are also serving the public which supports us with tax dollars by avoiding an unnecessary, large expenditure. But most important, we have trained in these 5 years over 300 physicians to practice medicine without resorting to this much overused drug * * *

Since there are over 500 doctors in training at Cook County Hospital one can assert that a significant number of physicians on the threshold of their training have a unique therapeutic advantage over their contemporaries.

Thus, it is quite possible—even less dangerous and much less expensive to practice medicine without the use of Darvon.

Further comment on the prospect of an imminent hazard ban was received from chief coroner of San Francisco, Dr. Boyd Stevens, in a letter to me dated January 9, 1979.

The experience of this office with propoxyphene preparations indicates that this is an abused drug with little analgesic quality and whose daughter compounds are of no significant analgesic property, but are potentially toxic.

Because of its frequency of abuse and because of its propensity for toxic results in relatively low doses when mixed with other compounds such as alcohol, the position of this office is that propoxyphene should be withdrawn from the market.

Barring the withdrawing of propoxyphene from the pharmaceutical market, we would support it being placed at a schedule II rating of the Control Substance Act.

In summary, exploiting doctors' desires for a safe and effective painkiller Lilly pushed Darvon 21 years ago as equally effective as codeine, nonaddicting and safer than codeine.

All three statements are false yet millions of Americans have used this expensive and weak painkiller, thousands have died as a result of its toxicity and Lilly has reaped well over one-half of a billion dollars from its sales.

The information that chronic use of Darvon leads to high blood levels of the toxic metabolite nor-propoxyphene has never been publicly acknowledged by Lilly, lest it might frighten doctors and patients from using the drug.

I hope these hearings provide any additional incentive still needed for the Government to act on Darvon as quickly as possible.

Thank you.

Senator NELSON. Thank you, Dr. Wolfe.

Mr. Edgar G. Davis, vice president for corporate affairs, Eli Lilly & Co., sent a letter to my office shortly before the hearings, which he has asked to have read into the record. I shall do so, and you may wish to comment on it.

The letter is dated January 31, 1979, and reads as follows:

DEAR SENATOR NELSON: We were dismayed by the reckless and irresponsible suggestion made by Dr. Wolfe at page 2 of his prepared statement that Lilly had not submitted to the FDA "critical information" with respect to certain dog studies conducted in 1976.

The facts are to the contrary. After the experiments were completed, in accordance with accepted research procedure, the scientists involved prepared an abstract of the work which contained all the critical information. This was published in 1977 in Federation Proceedings, Vol. 36, page 586. The authors presented their findings at the Federation meetings in March 1977. The abstract was submitted By Lilly to the FDA in the same month.

Following this, the scientists undertook the preparation of a manuscript for journal publication, expanding on the abstract. This manuscript was submitted in March 1978 to the Journal of Toxicology and Applied Pharmacology for consideration, was accepted for publication in May 1978, and will appear in the January 1979 issue of the Journal. While this time period may seem lengthy to a layman, it is consistent with the publication practices of scientific journals.

The abstract and the forum presentation included all the essential information on the experiments. Lilly takes strong exception to Dr. Wolfe's characterization and unwarranted insinuations.

Lilly, in more than a century of service to the medical profession and to the ill, has developed and maintained a merited reputation for integrity. The Company has always shared scientific information concerning its pharmaceutical products with the appropriate agencies of government. It does not withhold information bearing on the safety and efficacy of its products.

We respectfully request that this letter be read into the record during Dr. Wolfe's appearance today. We resent this unfair attack on Lilly's scientific integrity and public responsibility.

Dr. WOLFE. I would like to respond to that.

The statement is misleading, to be generous with it.

First of all, I have copies of the abstract that was sent in, the abstract they referred to, and that I referred to in the testimony.

The abstract was sent to the FDA, as I said in the testimony, and it did not contain critical information as I also said in the testimony.

The critical information I am referring to which is contained in the full report that was provided by a source in the company, is that the drug can cause second degree heart block. There is no mention in the abstract that the drug can cause second degree heart block.

Even though, as the company states in its letter that you just read, they submitted a copy of the manuscript to the Journal of Toxicology and Applied Pharmacology, they in fact did not submit a copy of the manuscript at least as of a couple of weeks ago to the FDA. Whereas I can well understand it may take some time to get a paper published, I think it is indefensible they did not submit to the FDA as they promised to do 2 years ago, the full study, including the fact it caused second degree heart block, therefore, I think that their statement is extremely misleading. The information I referred to was omitted from the abstract, and FDA, as I mentioned, is considering reprimanding the company for this, even though technically they cannot bring criminal proceedings against the company.

I would like to add one other thing which I left out.

Senator NELSON. Wait a minute.

I will ask the FDA to comment on that issue, as well, of course, as the Lilly Co., when they testify next Monday.

Mr. TWARDY. I would like to submit for the record a copy of the letter which was sent by Eli Lilly & Co. to the FDA and the abstract which accompanied it.

[Original copy of letter and abstract follow:]

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206

EDGAR G. DAVIS
VICE PRESIDENT
CORPORATE AFFAIRS

January 31, 1979

The Honorable Gaylord Nelson
Chairman
Select Committee on Small Business
United States Senate
Washington, D.C. 20510

Dear Senator Nelson:

We were dismayed by the reckless and irresponsible suggestion made by Dr. Wolfe at page 2 of his prepared statement that Lilly had not submitted to the FDA "critical information" with respect to certain dog studies conducted in 1976.

The facts are to the contrary. After the experiments were completed, in accordance with accepted research procedure, the scientists involved prepared an abstract of the work which contained all the critical information. This was published in 1977 in Federation Proceedings, Vol. 36, page 586. The authors presented their findings at the Federation meetings in March, 1977. The abstract was submitted by Lilly to the FDA in the same month.

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We respectfully request that this letter be read into the record during Dr. Wolfe's appearance today. We resent this unfair attack on Lilly's scientific integrity and public responsibility.

Respectfully yours,

Edgar G. Davis
Vice President
Corporate Affairs

Copies to members
of the Subcommittee

Mr. A. E. Crum

March 17, 1977

Food and Drug Administration
Bureau of Drugs, HFD 120
Attention: Document Control Room 10B-34
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: IND 1536 - Darvon-N®, propoxyphene napsylate, Lilly, with and without aspirin - Annual Report

The enclosed abstract concerning a pharmacology study represents the annual report. There is no new development-control or clinical information to be submitted at this time.

Very truly yours,

ELI LILLY AND COMPANY

H. A. Barnett, M.D.
Medical Advisor
Regulatory Affairs

HAB:bs

Enclosure

IND - 1656 - DARVON-N®, Propoxyphene Napsylate, Lilly

Twelve-Month Report

DEPRESSION OF CARDIAC CONDUCTION BY PROPOXYPHENE AND NORPROPOXYPHENE

The following abstract is a preliminary report of conduction depression produced by propoxyphene and norpropoxyphene. A complete presentation of this data will be submitted in a manuscript that is now being prepared.

PHARMACOLOGY

DEPRESSION OF CARDIAC CONDUCTION BY PROPOXYPHENE AND NORPROPOXYPHENE. Donald R. Holland* and Mitchell I. Steinberg. The Lilly Research Laboratories, Indianapolis, Ind. 46206

The centrally acting analgesic, d-propoxyphene (P), and its N-demethyl metabolite, d-norpropoxyphene (NP), are potent local anesthetics. Since local anesthetics depress cardiac conduction, we studied the effects of these agents on conduction in the canine heart both *in vivo* and *in vitro*. When P was infused intravenously into conscious dogs at doses of 2.1 to 21 μmole/kg (0.8 to 8 mg/kg), the P-R interval was prolonged in a concentration dependent manner. A 30% prolongation of the interval was observed at 21 μmole/kg. Norpropoxyphene (21 μmole/kg, i.v.), prolonged the P-R interval 17%. His bundle electrograms were recorded in pentobarbital anesthetized dogs pretreated with propranolol and atropine to block neurogenic influences. Intravenous administration of either P or NP prolonged conduction times in the AV node and infra-His conduction system. AV nodal conduction was prolonged 10% by P and NP at doses of 3.3 ± 0.5 μmole/kg and 6.5 ± 1.2 μmole/kg, respectively. Infra-His conduction was prolonged 10% by P and NP at doses of 17.1 ± 1.2 μmole/kg and 7.5 ± 2.8 μmole/kg, respectively. In isolated canine Purkinje fibers superfused *in vitro*, both agents depressed the maximum rate of rise of phase 0 of the action potential ($\dot{V}_{max}$) and shortened action potential duration. The concentrations that produced a 50% decrease in $\dot{V}_{max}$ were 2.5×10^{-5} M with P and 1.2×10^{-5} M with NP. Thus P and NP, like other local anesthetics, depress cardiac conduction in the canine heart, *in vivo* and *in vitro*.

Donald R. Holland, Ph.D.
Associate Sr. Pharmacologist
2/10/77

Dr. WOLFE. I mentioned briefly that doctors treat symptoms of pain.

It is one of the most common problems a person brings to the doctor, therefore a pain reliever that is very effective, that is safe, is something that physicians would reach for. The way the drug was originally promoted, I think, accounts for a lot of abuse, and I would like to refer to a current ad running in medical journals for Darvon, which I think is appalling.

This describes how the drug industry in this country promotes pharmaceutical products. It is a three dimensional picture of the word pain in reds and purples, with a woman draped over the letters, just for those wanting to see it.

This is how Lilly pushes Darvon, with obnoxious advertisements like this.

Senator MORGAN. Could you point it this way so we could see it?

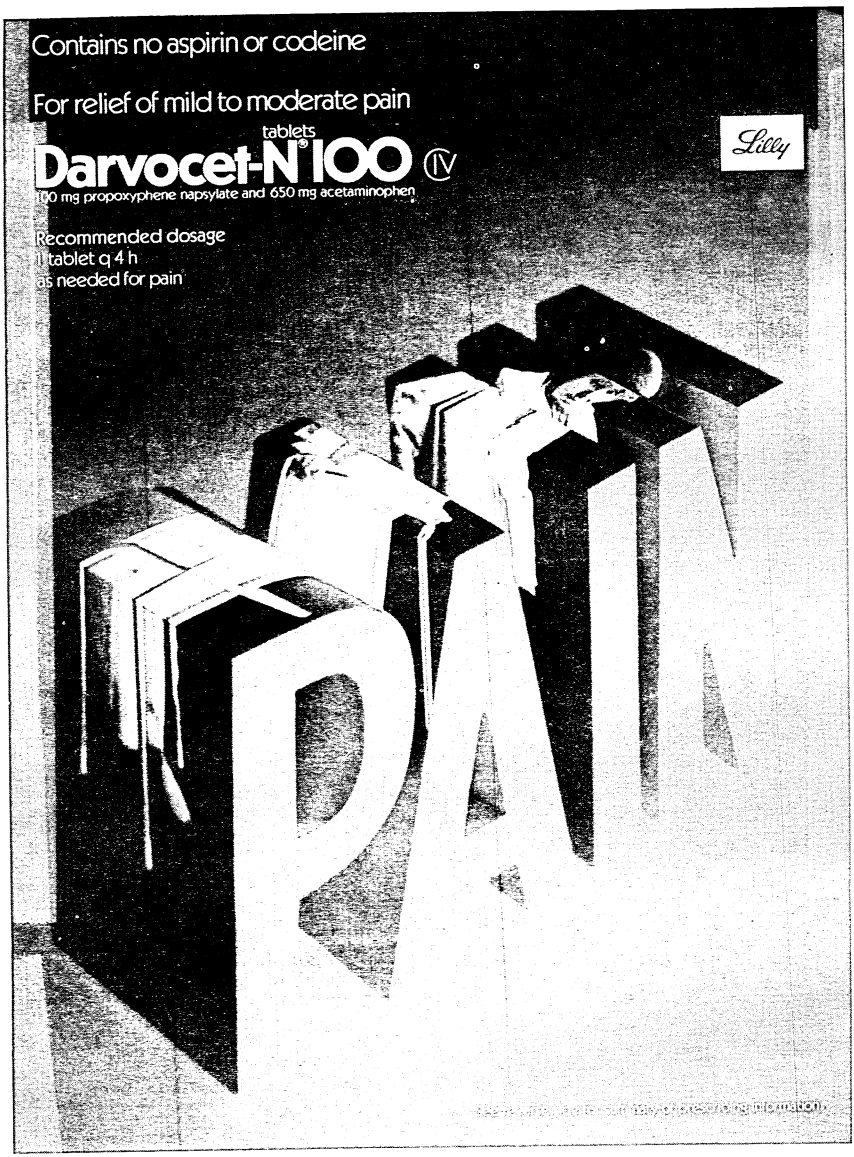
Dr. WOLFE. I think I will just pass it around.

The advertisement apparently works. It appears to me Darvon is much more advertised than any other painkilling drug.

Senator NELSON. Is this a 2- or 3-page ad?

Dr. WOLFE. It is a 2-page ad, and on the back are much smaller letters, some of them warning about the drug.

[The advertisement follows:]


Contains no aspirin or codeine
For relief of mild to moderate pain
tablets
Darvocet-N® 100 Ⓒ IV
100 mg propoxyphene napsylate and 650 mg acetaminophen
Recommended dosage
1 tablet q 4 h
as needed for pain
Lilly
PAIN

(iv

Darvocet-N® 100

propoxyphene napsylate with acetaminophen

Description: Each tablet of Darvocet N 50 contains 50 mg propoxyphene napsylate and 325 mg acetaminophen Each tablet of Darvocet N 100 contains 100 mg propoxyphene napsylate and 650 mg acetaminophen

Indication: These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen

Warnings: C N S Additive Effects and Overdosage -- Propoxyphene in combination with alcohol, tranquilizers, sedative hypnotics, and other central-nervous system depressants has additive depressant effects, and the patient should be so advised Patients taking this drug should be warned not to exceed the dosage recommended by their physician Toxic effects and fatalities have occurred following over doses of propoxyphene alone and in combination with other central nervous-system depressants The majority of these patients have had previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, or other C N S active drugs Caution should be exercised in prescribing unnecessarily large amounts of propoxyphene for such patients

Drug Dependence – Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine

Usage in Ambulatory Patients – Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery The patient should be cautioned accordingly.

Usage in Pregnancy – Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards

Usage in Children – Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S depressants, including alcohol.

Adverse Reactions: The most frequent adverse reactions are dizziness. sedation, nausea, and vomiting These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances

The chronic ingestion of propoxyphene in doses exceeding 800 mg per day has caused toxic psychoses and convulsions

Cases of liver dysfunction have been reported.

Administration and Dosage: A narcotic prescription is not required

These products are given orally The usual dose is 100 mg propoxyphene napsylate and 650 mg acetaminophen every four hours as needed for pain

[081777A]

Additional information available to the profession on request from Eli Lilly and Company,

Lilly

Indianapolis, Indiana 46206

Eli Lilly and Company, Inc
Carolina, Puerto Rico 00630

800383

Senator NELSON. You have a letter with your testimony from Cook County Hospital, and that will be made part of the record.

[The letter follows:]

COOK COUNTY HOSPITAL,
Chicago, Ill., January 23, 1979.

SYDNEY WOLFE, M.D.,
Health Research Group,
Washington, D.C.

DEAR DOCTOR WOLFE: On July 1, 1974, Darvon in all its forms was banned from the prescription options for all physicians working in the outpatient setting of our hospital (the General Medical Clinic of Fantus Clinic). This is the largest clinic by far in the Cook County Hospital complex seeing on an average of 200 patients per day. The doctors are predominantly members of the house staff; each of our 160 Department of Medicine trainees attends that clinic one session per week. The same rules apply to other specialty clinics under the jurisdiction of the Department of Medicine which average another 200 patient encounters per day.

The reasons for eliminating Darvon from the drug list included high cost and absence of any therapeutic superiority over aspirin and aspirin related drugs for its legitimate indications. Another, more serious concern was our observation, in this large public hospital, that Darvon was increasingly utilized as an illicit drug by persons who had become dependent upon it. We concluded that an agent devoid of any significant, unique value which was the object of dangerous abuse by growing numbers of people, had no place on our hospital outpatient formulary.

While I feel that we served our patients well by avoiding this potentially dangerous drug, we've also served the public which supports us with tax dollars by avoiding an unnecessary, large expenditure. But most important, we have trained in these five years over 300 physicians to practice medicine without resorting to this much overused drug.

Finally, it is most interesting and gratifying to note that following the excellent experience of the Department of Medicine outpatient clinics (elimination of this drug without physician or patient difficulty), the Drug and Formulary Committee of the entire hospital decided in June 1977 to delete the drug from the hospital formulary (see attached communication from Mr. E. H. Stinebaugh, Director of Pharmacy Services). The entire medical staff had so diminished its "dependence" on Darvon that it took nearly 18 months for the existing supplies to be exhausted Since there are over 500 doctors in training at Cook County Hospital, one can assert that a significant number of physicians on the threshold of their training have a unique therapeutic advantage over their contemporaries

Sincerely yours,

QUENTIN D. YOUNG, M.D.
Chairman, Department of Medicine.

Attachment.

COOK COUNTY HOSPITAL,
Chicago, Ill., March 8, 1978.

Memo to: Medical Staff.

From: Ernest H. Stinebaugh, Director, Department of Pharmacy Services.

Re: Propoxyphene HCl (Darvon).

At the Drug and Formulary Committee Meeting in June, 1977 propoxyphene HCl was deleted from the formulary. Provisions were made at that time to continue using existing stocks until depleted. The stocks of propoxyphene HCl are now near depletion and the drug will no longer be available on prescription in Cook County Hospital or health centers.

The committee made its decision based upon several review articles:

1. Drug Therapy Review: Propoxyphene, A Review, Miller RR et al, *American Journal of Hospital Pharmacy*, Volume 34, April, 1977, page 413ff

2. Propoxyphene HCl A Critical Review, Miller RR, *Journal of the American Medical Association*, Volume 213, Number 6, August 10, 1977, page 996ff

3. *Medical Letter*, Volume 12, Number 2, January 23, 1970, page 5 as well as considerations that

4. Propoxyphene is a controlled substance and the burden of providing proof of use and distribution outweighs its usefulness,

5. The potential encouragement of street abuse is great by having it generally available from Cook County Hospital and clinics.

Published data suggests that alternate therapy is 600mg of aspirin or acetaminophen. Potent analygesics also available are acetominophen with codeine and aspirin with codeine. I refer you to page 14 in the Drug List for a complete listing of analygesics on formulary.

Senator NELSON. Any further questions?

Senator MORGAN. Dr. Wolfe, I did not hear all of your testimony, and I apologize for that.

Will you tell me the extent of your research, how did you arrive at your conclusions?

Dr. WOLFE. Which conclusions are you speaking of?

Senator MORGAN. All of them, with regard to Darvon, and whether or not it was more effective, or less effective than aspirin and the other drugs, are these based upon publications, or are they based upon independent research by your group, or by public citizens health research groups?

Dr. WOLFE. Well, all of the work, which is much more detailed in the petition to the Justice Department, is based upon a review of published studies on the safety and on the effectiveness, of the drug.

In addition, we used information supplied by the Justice Department Drug Abuse Warning Network. Any statement that we make concerning its effectiveness with respect to aspirin and anything else, is based on a large number of published studies that we have reviewed.

One of the witnesses this morning, in addition to reviewing the published literature has also done studies himself, comparing Darvon with other analgesics, and I think reaches the same conclusions as I do.

Senator MORGAN. I am asking, what have you done? Have you done any research?

Dr. WOLFE. I have reviewed the published literature and used information from the Justice Department to reach the conclusions that I have.

Senator MORGAN. Do we have a copy of the petition, Mr. Chairman, that you have alluded to?

Senator NELSON. The committee has a copy of the petition that has been filed, and it will be made a part of the record.

Senator MORGAN. It would be of interest to me, Doctor, to know what your background is, so that I can determine how much weight to give your evaluation of other publications.

Dr. WOLFE. Let me briefly go over it. My training is in internal medicine.

I was on the staff of the National Institutes of Health for 5 years, doing medical research on both clinical and laboratory problems.

I have published a fair number of papers on various kinds of research that I have done.

Senator MORGAN. That is all I have, Mr. Chairman.

Senator NELSON. Any other questions?

Mr. TWARDY. Dr. Wolfe, you indicated there was no effectiveness requirement in 1957 when Darvon was first marketed.

Dr. WOLFE. That is correct.

Mr. TWARDY. However, pursuant to a law passed in 1962, was not the FDA required to study the effectiveness of drugs marketed prior to 1962?

Dr. WOLFE. That is right.

In doing that, for Darvon, because it was a pre-1962 drug, the National Academy of Sciences, particularly for the 32-milligrams, the smaller size Darvon which was then widely used, found that it really was not much better than a placebo.

Mr. TWARDY. But the FDA did allow Darvon to stay on the market, and gave a blanket approval to the effectiveness of the 65-milligram dose, did it not?

Dr. WOLFE. That is correct, because, as I stated, as long as it could be shown that that form, the 65-milligrams, was better than a placebo, that would meet the test of effectiveness.

Mr. TWARDY. So in short, the FDA did deem the 65-milligram dosage of Darvon to be effective?

Dr. WOLFE. Right, more effective than a placebo, and therefore meeting the law.

Mr. TWARDY. I might have missed this, but to whom is the advertisement that Lilly has here for Darvon circulated? Is it to the public as a whole or just to doctors?

Dr. WOLFE. There is an ad that appears—I have seen that same ad in five or six medical journals in the last month or so.

Mr. TWARDY. But it is circulated then to the medical profession?

Dr. WOLFE. That is right. I think that if physicians saw this kind of ad, if patients saw that kind of ad, they would be much more inclined to use Darvon.

Mr. TWARDY. That is all; thank you.

Senator NELSON. Thank you, Dr. Wolfe.

Dr. WOLFE. Thank you.

[The prepared statement of Dr. Wolfe follows:]

TESTIMONY OF SIDNEY M. WOLFE, M.D., PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

Senator Nelson and members of the subcommittee: Thank you for the invitation to discuss our petitions to ban or severely restrict the use of propoxyphene, most commonly known as Darvon.

In the November petitions, we pointed out that Darvon led all other prescription drugs in the annual number of drug deaths and, as was pointed out by N. Kozel of the National Institute for Drug Abuse, Darvon is probably related to even more deaths per year than heroin and morphine combined.

Since the original petitions we have obtained more information—particularly about the toxicity in animals and humans of propoxyphene and especially its main metabolite, norpropoxyphene. We have also learned that a substantial portion of Darvon deaths are not due to suicide but are accidental and often occur in people chronically using the drug for pain or, in some cases, for its euphoric effects.

PROPOXYPHENE AND NOR-PROPROXYPHENE BLOOD LEVELS IN CHRONIC DARVON USERS

When people use propoxyphene (PX), the drug is metabolized by the liver to nor-propoxyphene (NPX). Whereas the ½ life of PX in the blood is only 12 hours (meaning the time it takes for the drug to fall to half of its highest level), the main metabolite, NPX, stays around much longer, having a half-life of 38 hours. Because of this long half-life, people using Darvon on a chronic basis accumulate large amounts to the metabolite NPX in their blood.

Much of the early human toxicology on PX looked just at blood levels of the drug itself and unless the blood level was 1 or 2 micrograms per milliliter (ml.) of blood, or more, the death was often not attributed to PX. In cases of

suicide where death occurs shortly after ingestion of huge numbers of pills, the blood PX level is, in fact, usually above 1 or 2 micrograms and milliliter with much lower levels of NPX.

In chronic users, however, there is much more NPX than PX in the blood. Someone regularly taking as little as 2 pills (65 milligrams per pill) 3 times a day can get a blood PX level of .68 micrograms per ml. but an NPX level of 1.2 micrograms per ml.[1]

A cancer patient, chronically using two 65 mg. pills every four hours (recommended dose is 1 pill every four years) had a PX blood level of .87 micrograms per ml. and a NPX level of 3.1.[1] The fact that people using Darvon at or slightly above the recommended dose can get NPX blood levels of 1–3 micrograms per ml. is particularly alarming in view of the finding that:

(a) in many cases of accidental death due to Darvon, the blood NPX levels are in this 1 to 3 range with PX levels much lower (often less than 1) as in the patients cited above,[2] and

(b) comparable blood levels (1 to 3 micrograms per ml.) of NPX in animals can cause significant blocking of conduction through the heart, a toxicity which can lead to arrhythmias and death.

Although the medical literature, as long as 15 years ago, contained many cases of Darvon poisoning in which patients had abnormal electrocardiograms showing an inhibition of electrical condition thru the heart and although many Darvon deaths were said to be of cardiac origin, the first animal study on the cardiac toxicity of PX[1] and NPX was not done until 1976 by Lilly.

LILLY STUDY NEVER PUBLISHED NOR SENT TO FDA

From a source within Lilly, we have obtained an 11 page progress report of dog experiments, dated February 16, 1976 to August 15, 1976. On March 17, 1977, a short ½ page abstract of this study—omitting critical information—was sent by Lilly to FDA with a note that "a complete presentation of this data will be submitted in a manuscript that is now being prepared."

As of several weeks ago, when I forwarded this report to FDA and almost 2 years after Lilly's promise to FDA, the "complete presentation" had not been sent to FDA by Lilly nor has it ever been published. (A stamp on the top of the report says it should "not be published or disclosed to unauthorized persons without specific written permission of Dr. I. H. Slater.")

The study showed that both PX and NPX could cause inhibition of cardiac electrical conduction in the 1–3 micrograms per ml. range and that NPX was more potent than PX in one important type of inhibition.

Although the study says the blood concentrations of PX and NPX were "substantially higher than required for analgesia" (pain relief) the levels of NPX causing inhibition in these drugs were in the same 1–3 microgram per ml. range which can be seen in people who chronically use PX. (See p. 2 of testimony).

DANISH STUDIES ON CARDIAC TOXICITY

A recently published Danish study[3] also shows that NPX in the 1–3 microgram per ml. range in rabbits can cause significant delay or inhibition of cardiac conduction and cardiac arrhythmias also were seen.

An earlier Danish study of 11 cases of Darvon poisoning[4] showed that 4 patients had cardiac conduction delays similar to those described above with blood NPX and PX levels of:

NPX:	
0.78	0.47
0.39	.74
0.79	.51
0.35	.23

(One of these patients also had ingested a substantial amount of ethyl alcohol but this is not known to cause the above-mentioned cardiac conduction delays.)

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[1] Verbeley and Inturrisi, J. Chromatography *75:* 195, 1973.
[2] Personal Communication, Dr. Boyd Stevens, Coroner, San Francisco and Dr. Larry Lewman, Deputy Coroner, State of Oregon.
[3] Lund-Jacobsen, Acta. pharmacol, et toxicol., *42*, 171, 1978.
[4] Gustafson and Gustafson, Acta. Med. Scand. *200*, 241, 1976.

BLOOD NPX LEVELS IN ACCIDENTAL DEATHS

According to both Dr. Larry Lewman, Deputy Coroner of Oregon, and Dr. Boyd Stevens, Coroner of San Francisco, most of the Darvon deaths are not suicides but accidents. One of the criteria for making this decision is an NPX blood level as high or higher than the PX level, often suggesting chronic use of PX.

Blood NPX levels in such accidental deaths are often slightly less than 1, 1, 2, 3 or 4 micrograms per ml. of blood with PX levels often less than 1.

DARVON MARGIN OF SAFETY IS TOO LOW

The margin of safety or therapeutic index of a drug is the ratio between the amount needed to achieve the therapeutic effect (in this case alleged relief of pain) and the amount causing toxicity. According to Danish toxicologist Dr. J. Simonsen [5], Darvon has a "narrow therapuetic index": He says that "just four times the ordinary therapeutic dose can produce highly serious poisoning."

San Francisco Chief Coroner Dr. Boyd Stevens told me that "if you double the Darvon dosage and take just 1 to 2 (bar) drinks, you can get into the toxic or lethal range." Dr. Stevens points out that partly because of its relative weakness as a painkiller, patients may well be inclined to take 2 pills (or more) instead of 1. He says, therefore, that many of the Darvon accidental deaths are not abuse—in the strict sense.

This very low margin of safety is very likely related in many cases to the accumulation, as described above, of the toxic metabolite norpropoxyphene (NPX) in people regularly using the drug. In the above-mentioned study by Simonsen, he discusses the fact that we may be just seeing the tip of the iceberg as far as Darvon deaths. The study describes 2 elderly people found dead with no evidence of suicide whose deaths would otherwise have been attributed to natural causes but for a Danish law requiring autopsy on those dying alone. Subsequent toxicologic analysis showed both to be Darvon deaths.

DARVON VS. MORE EFFECTIVE PAIN-RELIEVERS

Since Darvon's effectiveness in relieving pain is somewhere between that of aspirin (or acetaminophen as in Datril, Tylenol) and a placebo and substantially less than that of codein (in Schedule II and III), it is of interest to look at the number of deaths and the death rate of these preferable analegsics in comparison to Darvon.

Drug and Deaths: 1977 [6]	*Deaths Per Million Prescriptions* [7]
Darvon—590	19
Codeine—255	5
Aspirin [8]—150	<1
Acetaminophen [8]—77	<1

PREDICTABLE INADEQUACY OF SCHEDULE IV

When the possibility of controlling Darvon by putting it into the weak control of Schedulue IV, was first raised in 1973, Lilly responded by saying that if the drug should wind up in Schedule IV, despite its protests, "we believe it wouldn't have any material effect on sales of the product." [9]

In the year before Darvon was put into Schedule IV March 1976–February 1977, there were 459 deaths related to its use. In the first year of Schedule IV (March 1977–February 1978), the number was 510. Although there appears to be a decrease in deaths during the latter part of 1978, these data underestimate the eventual number of reported deaths since all 1978 reports are not completed and sent to DEA until well into 1979.

Although there has been an apparent but slight decrease in emergency room visits involving Darvon, this is not accompanied by any evidence yet of a decrease in fatalities.

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[5] Ugeskr. Laeg. *137*(44) 2605–2609. 1975.
[6] DAWN Quarterly Report January–March 1978.
[7] 1977 Prescriptions filled from National Prescription Audit, I.M.S.
[8] 1977 Retail sales of Aspirin of $500 million and acetaminophen, $150 million—assume average cost of $1 for aspirin, $1.50 for acetaminophen and use death per million bottles.
[9] Wall Street Journal, Aug. 6, 1973.

IMMINENT HAZARD BAN

As stated in the petition to HEW, rescheduling Darvon in Schedule II only makes sense if it is possible to identify a group of people for whom the substantial risks of the drug are outweighed by the questionable benefits, taking into account the availability of aspirin, codeine, and acetaminophen, all safer and more effective. I am still unable to identify such a group of people and therefore believe an imminent hazard ban is the preferable way of meeting this serious problem.

CONSEQUENCES OF A BAN

In a letter to me from Dr. Quentin Young, Chief of Medicine at Cook County Hospital in Chicago, dated January 23, 1979 (see attachment 1), he states that Darvon was banned from the medical clinics there in 1974 and from the entire hospital in June 1977. Dr. Young said:

"The reasons for eliminating Darvon from the drug list included high cost and absence of any therapeutic superiority over aspirin and aspirin related drugs for its legitimate indications. Another, more serious concern was our observation, in this large public hospital, that Darvon was increasingly utilized as an illicit drug by persons who had become dependent upon it.

"We concluded that an agent devoid of any significant, unique value which was the object of dangerous abuse by growing numbers of people, had no place on our hospital outpatient formulary.

"While I feel that we served our patients well by avoiding this potentially dangerous drug, we're also serving the public which supports us with tax dollars by avoiding an unnecessary, large expenditure. But most important, we have trained in these five years over 300 physicians to practice medicine without resorting to this much overused drug. * * *

"Since there are over 500 doctors in training at Cook County Hospital, one can assert that a significant number of physicians on the threshold of their training have a unique therapeutic advantage over their contemporaries."

Thus, it is quite possible—even less dangerous and much less expensive to practice medicine without the use of Darvon.

Further comment on the prospect of an imminent hazard ban was received from Chief Coroner of San Francisco, Dr. Boyd Stevens, in a letter to me dated January 9, 1979.

"The experience of this office with propoxyphene preparations indicates that this is an abused drug with little analgesic quality and whose daughter compounds are of no significant analgesic property, but are potentially toxic.

"Because of its frequency of abuse and because of its propensity for toxic results in relatively low doses when mixed with other compounds such as alcohol, the position of this office is that Propoxyphene should be withdrawn from the market.

"Barring thte withdrawing of Propoxyphene from the pharmaceutical market, we would support it being placed at a Schedule 2 rating of the Control Substance Act."

SUMMARY

Exploiting doctors' desires for a safe and effective painkiller Lilly pushed Darvon 21 years ago as equally effective as codeine, non-addicting and safer than codeine. All three statements are false yet millions of Americans have used this expensive and weak painkiller, thousands have died as a result of its toxicity and Lilly has reaped well over ½ billion dollars from its sales.

The information that chronic use of Darvon leads to high blood levels of the toxic metabolite norpropoxyphene has never been publicly acknowledged by Lilly, lest it might frighten doctors and patients from using the drug.

I hope these hearings provide any additional incentive still needed for the government to act on Darvon as quickly as possible.

Thank You.

Senator NELSON. Next we will have a panel of witnesses.

We call Dr. C. G. Moertel, Mayo Clinic, Rochester, Minn.

Dr. Page Hudson, chief medical examiner, Chapel Hill, N.C.

Dr. Arthur J. McBay, chief toxicologist, office of the chief medical examiner, Chapel Hill, N.C.

And Dr. Larry V. Lewman, pathologist and medical examiner of Multnomah County, Oreg., and deputy State medical examiner, State of Oregon.

Would you mind all coming up and joining in a panel.

First, I will ask Mr. Charles Moertel to present his testimony.

Before we begin, I wonder, for the purposes of keeping an accurate record, starting at my far left, if each of you would identify yourselves for the reporter, so that whenever you speak, he will attribute the comments correctly in the printed record.

Dr. McBAY. Dr. McBay.

Dr. MOERTEL. Dr. Moertel.

Dr. LEWMAN. Dr. Lewman.

Dr. HUDSON. Dr. Hudson.

Senator NELSON. Dr. Moertel, you may proceed.

Would you mind identifying your specialty in the field of medicine?

STATEMENT OF CHARLES G. MOERTEL, M.D., MAYO CLINIC, ROCHESTER, MINN.

Dr. MOERTEL. Yes.

[Résumé follows:]

CURRICULUM VITAE

Name: Charles G. Moertel, M. D.

Date and Place of Birth: October 17, 1927, Milwaukee, Wisconsin

Marital Status: The former Virginia Sheridan. Four children

Present Position: Chairman, Department of Oncology, Mayo Clinic
Director, Mayo Comprehensive Cancer Center
Professor of Oncology, Mayo Medical School

Education:

1945 - 1946	University of Illinois Chicago, Illinois
1948 - 1949	Northwestern University Evanston, Illinois
1949 - 1953	University of Illinois Chicago, Illinois B.S., M.D.
1953 - 1957	University of Minnesota Minneapolis, Minnesota M.S.

House Staff Training:

1953 - 1954	Los Angeles County General Hospital Los Angeles, California. Internship
1954 - 1957	Mayo Foundation Rochester, Minnesota Residency - Internal Medicine
1957 - 1958	Mayo Clinic Rochester, Minnesota Assistant to the Staff

Certification and Licensure:

1962	Am. Board of Int. Med.

Fellowship Training:

Dates as above	As above

Military Service:

1946 - 1947	U. S. Army

Professional Experiences:

1958 - present	Mayo Clinic Rochester, Minnesota Consultant, Oncology Staff
1958 - present	St. Mary's, Methodist Hospitals Rochester, Minnesota Staff, Oncology
1971 - 1974	Associate Editor, Cancer Yearbook
1972 - 1974	Chairman, Gastrointestinal Cancer Committee Eastern Cooperative Oncology Group
1973 - present	Cochairman, Gastrointestinal Tumor Study Group, DCT, NCI
1973 - present	Phase I Study Group, DCT, NCI
1974 - present	Consultant, Medical Letter
1974 - present	Oncologic Drug Advisory Committee, FDA
1974 - 1977	Committee on Cancer Immunotherapy, Immunology Branch, NCI
1975 - 1978	Board of Directors, American Society for Clinical Oncology
1975 - present	Editorial Board, Cancer
1976 - present	Associate Editor, Cancer Medicine
1976 - present	Special Advisory Committee, Sec'y Califano, DHEW
1978 - present	President-elect, American Society of Clinical Oncology
1978 - present	Chairman, Clinical Program Subcommittee, American Association for Cancer Research
1978 - present	Council on Cancer, American Medical Association
1978 - present	Board of Directors, Society for Clinical Trials

Professional Societies:

American College of Physicians
American Gastroenterologic Association
American Association for Cancer Research
American Society of Clinical Oncology
Sigmi XI
Society of Surgical Oncology
Society for Clinical Trials

Educational Experience:

1959 - 1963	Graduate School University of Minnesota Minneapolis, Minnesota Instructor in Medicine
1963 - 1968	Assistant Professor of Medicine
1969 - 1972	Associate Professor of Medicine
1972 - 1976	Professor of Medicine Mayo Medical School
1976 - present	Professor of Oncology Mayo Medical School

Research Interests:

1955 - 1956	Pathologic Anatomy
1957 - 1958	Clinical Pathology - Radioisotope Studies
1958 - present	Clinical Research - Cancer Chemotherapy and Clinical Oncology Clinical Pharmacology

Senator NELSON. Thank you, Dr. Moertel.

You may present your statement. It will be printed in full in the record, and you may present it as you wish.

Dr. MOERTEL. As you can see from curriculum vitae, I am a cancer doctor. I have been devoted to the care of cancer patients for a lot of years. We do cure many cancer patients, and there has been substantive progress in clinical research, but with all this, we must still admit that most patients afflicted with cancer will die of their disease. For these patients our primary concern must be they die in dignity and in comfort.

The single most overriding responsibility we have as physicians is the relief of the pain.

Unfortunately, in this vital area, we, as physicians frequently perform rather poorly.

Our medical schools' instruction in the practical use of drugs is often inadequate.

In our judgment in prescribing drugs for pain, it is quite comparable to the public's judgment in purchasing over-the-counter drugs for pain.

Both are largely governed by advertising. We, as doctors, are no less vulnerable than the public-at-large to the persuasive influence of Madison Avenue.

For vivid evidence of our confusion in this regard, you only have to look at the Physicians Desk Reference. For those of you not familiar with this, the manual is distributed free of charge to all physicians each year by the Pharmaceutical Manufacturers Association, and it lists all prescription drugs promoted by pharmaceutical companies.

In the 1978 edition, there were 149 drugs advertised to be given by mouth for relief of pain.

More than a decade ago, because we were disturbed by our ineptitude in the management of pain of the cancer patient, we initiated at the Mayo Clinic carefully controlled research studies to evaluate the relative effectiveness of the many medications for pain that were available to us.

Senator NELSON. Doctor, before you move to your next point, back to the 149 drugs advertised in the Physicians Desk Reference: Do you mean there are 149 that were identified as analgesics of one kind or another, each by a different name?

Dr. MOERTEL. Many were by different names, many were different combinations of comparable ingredients.

Senator NELSON. But they had a different name?

Dr. MOERTEL. They had different brand names. There were some with different consistency, and many times they were quite comparable in consistency.

Senator NELSON. Of the 149, how many represented different compounds?

I realize you have Darvon compound, which may be propoxyphene, and then you have aspirin and codeine, and you have all of these, but how many different pain relieving combinations were there in these 149 named analgesics?

Dr. MOERTEL. Yes; well, of course, there are so many combinations of individual drugs, but as far as individual drugs, I would estimate

there are probably approximately 15 drugs of the analgesic category and probably about 12 drugs of the narcotic category, that go into the various mixtures that make up this 149.

Senator NELSON. Some of the 149, I take it, were over-the-counter, and some were prescription drugs, is that correct?

Dr. MOERTEL. That is right.

Senator NELSON. Of those that were over-the-counter, how many involve drugs that we all hear of all of the time?

Dr. MOERTEL. The over-the-counter drugs at the present time primarily involve aspirin or acetaminophen. These are the bases for most of the over-the-counter drugs.

To these may be added a number of variations. Caffeine may be added to these, phenacetin is occasionally added, although not too frequently anymore. Occasionally the antihistamines are added for a sedative effect along with an analgesic agent, but almost all of them are based on either a primary aspirin base or primarily an acetaminophen base.

Senator NELSON. Thank you.

Dr. MOERTEL. More than a decade ago, because we were disturbed by our ineptitude in the management of pain of the cancer patient, we initiated at the Mayo Clinic carefuly controlled research studies to evaluate the relative effectiveness of the many medications for pain that were available to us.

Our only vested interest was our patients in pain. These studies were not paid for by any drug company.

To insure that the results of these studies could not be in any way influenced by us or by preconceived ideas of our patients, we double-blinded the studies.

By this, I mean that all of the pain medications we gave to the patients looked exactly alike and were identified only by code number, so that neither we nor the patient could tell which was which until the study was over.

The drugs were administered in randomized sequences and we only broke the code when the entire study was complete.

Senator NELSON. So neither the patient nor the prescribing physician knew the drug he was giving?

Dr. MOERTEL. That is correct.

They were entirely blinded both to us and to the patients.

Now, in our first study, which is displayed on the chart on the easel, we looked at analgesic drugs in their pure form, and in this study we compared nine different analgesics as well as placebo or sugar pill.

This study involved close to 600 drug evaluations, and our results with the four drugs that are pertinent to this hearing discussed in this graph.

As you can see in the lower part, even with cancer pain, there will be a substantial number of patients who claim relief with sugar pills.

Darvon use alone showed some advantage over sugar pills, but this was small and it was not statistically significant.

That is the difference which could easily have occurred by accident.

Acetaminophen or APAP, commonly marketed as Tylenol or Datril, showed a much more substantial degree of relief; and surprisingly, leading the pack, two simple aspirin tablets.

The superiority of aspirin over Darvon was statistically significant, and by that I mean that the odds are 20 to 1 that this difference did not occur by chance alone.

These results were quite startling to us because at that time Darvon led the market in prescription drug sales.

It can reasonably be argued that although interesting, these results really are not a fair evaluation of Darvon.

Although Darvon is sold in pure form, it is usually marketed in combination with aspirin or APAP, or with APC as the so-called Darvon compound.

In our second study we, therefore, looked at aspirin alone compared to aspirin plus a variety of other drugs that are commonly marketed in aspirin containing drug combinations.

This study involved 100 patients in 1,000 separate drug evaluations.

In this chart, table 2, you can see that again aspirin showed a significant advantage over placebo. The addition of a full dose of Darvon to aspirin, however, provided essentially no improvement in pain relief. You can also see that within this same study it was demonstrated that two prescription drugs did provide better relief than aspirin alone, and these are the combinations of either Talwin—pentazocine—or codeine with aspirin.

Senator NELSON. These are drugs containing aspirin?

Dr. MOERTEL. This is a combination of Talwin plus aspirin, or a combination of codeine plus aspirin, and also a combination of Darvon plus aspirin.

Senator MORGAN. What is Talwin?

Dr. MOERTEL. Talwin is a trade name. It is a narcotic antagonist, which has been found to have some analgesic activity as well.

It was demonstrated that the standard and time-honored codeine-aspirin combination also showed a statistically significant advantage to the Darvon-aspirin combination, again the odds better than 20 to 1 that this difference did not occur by accident.

Based on our results we would have to conclude that if Darvon alone has any pain-relieving effect, this is trivial and simply does not match up to common, inexpensive over-the-counter drugs.

We must also conclude that the combination of Darvon with aspirin holds no advantage to aspirin alone, and if a patient requires a stronger analgesic the physician should prescribe some other more effective drug regimen.

These, however, are just the results from a single institution; and although we feel our studies were of sound design and conducted meticulously and analyzed without bias, it is possible that there could be some unrecognized distorting quirk in our methodology or that cancer pain is not representative of other types of pain.

We only really feel comfortable with clinical experimental results when they are confirmed by others.

Over the remainder of my testimony I would like to review all of the published medical literature of which I am aware that pertains to the clinical evaluation of Darvon as an analgesic agent.

Here I am only going to refer to the controlled, randomized, double-blind studies.

When your end point of a study is as subjective as pain relief, these are the only kind of studies you can believe.

In all, we found 34 such studies involving various types of pain, and these are listed in the bibliography which I have supplied.

In table 3 I have displayed the results of the 23 studies in which standard doses of Darvon alone were compared with placebo.

You can see that none of the studies favored sugar pills. In four of the studies there was essentially no difference between Darvon and sugar pills.

In seven the results favored Darvon but the difference was not statistically significant.

Our first study is included in these. In 12 of the 20 studies Darvon was favored and the results were statistically significant.

Based on these overall results it is reasonable to conclude that Darvon alone does have some analgesic activity although it is not very striking.

If, for example, aspirin alone had been tested in the 23 study populations of patients with relatively mild pain, it could be reasonably anticipated that aspirin would have been strongly favored in all 23.

In the next chart, table 4, I have displayed the results of 14 studies in which Darvon alone at standard doses was compared to common over-the-counter drugs—aspirin alone, acetaminophen or APAP alone, or APC.

Among this group there were no studies favoring Darvon, in one study there was no difference, and in the remaining 13 of the 14 studies the over-the-counter drugs were favored over Darvon.

In seven of these the differences were statistically significant.

In table 5, I have shown the studies involving standard doses of Darvon in combination with aspirin, APAP, or APC compound.

The results of these combinations are compared to the results of the over-the-counter drugs used alone with the addition of Darvon.

Three studies favored Darvon combinations, three favored the over-the-counter drugs used alone, and 6 of the 12 studies showed no difference.

It is of interest that there are two other studies of this kind that have not appeared in the medical literature although they have been highly publicized in lay media.

It seems that some admen at a proprietary pharmaceutical company must have been looking at the overall Darvon literature and decided they could make a real good sales pitch by showing their over-the-counter analgesic was just as good as Darvon compound.

So they proceeded to contract out for two clinical research studies and that is exactly what they showed.

Perhaps you remember the subsequent ads that appeared in the media displaying an Anacin tablet side by side with a Darvon compound capsule and accompanied by the advertising claim that Anacin had been shown in two medical studies to provide just as much relief as the high-priced prescription item.

Senator NELSON. May I ask before you go to the next paragraph, if I recall you correctly, it was only after the addition of the acetamino-

phen or aspirin to the Darvon that you found some studies to show it more effective? Is that correct?

Dr. MOERTEL. When acetaminophen or APC or aspirin were added to Darvon, most studies showed no difference to the over-the-counter drugs used alone.

There were three that showed an advantage for Darvon with over-the-counter combination, there were three that showed the advantage for the over-the-counter preparation used alone.

Senator NELSON. My question was, is it that Darvon with aspirin or acetaminophen then showed a difference over Darvon alone? Is that not correct?

Dr. MOERTEL. No; I did not display any studies of this kind.

There are studies of this kind that have been reported in the literature that do show that addition of aspirin or APC to Darvon does produce an improvement in pain effect over Darvon alone, but these were not displayed in my charts or in the material which I have presented to you.

Senator MORGAN. Dr. Moertel, if I follow you correctly, then your conclusions are that the ad compared Anacin, an over-the-counter drug, as being as good as Darvon, is that correct?

Dr. MOERTEL. Yes.

Senator NELSON. I did not hear that.

Dr. MOERTEL. I think it was predicted ahead of time that this would be shown, as the research studies were contracted.

Senator MORGAN. What I was saying, Mr. Chairman, that the witness addressed those ads that say that Anacin or other aspirin, which are over-the-counter drugs, are just as good as Darvon.

Senator NELSON. The evidence from your studies showed that they are better than Darvon, did they not—that aspirin alone or acetaminophen alone is more effective?

Mr. MOERTEL. Than Darvon alone, that is correct, but when Darvon is added to the aspirin, then it comes out about the same as aspirin.

Senator MORGAN. I have seen in the literature Darvon-N or Darvon-T.

What does it mean?

Dr. MOERTEL. The original preparation of propoxyphene as it was marketed in 1957, was a hydrochloride compound.

More recently, Darvon napsylate or Darvon-N has been prepared. Darvon napsylate is just another tag that is chemically put on the end of the Darvon molecule.

It does not in any way influence the analgesic effect of Darvon, and that has been proven repeatedly.

It was put on the market, because it provides a more stable tablet formulation with aspirin. You could mix it up in the same compressed capsule with aspirin, better than you can the hydrochloride form.

Senator MORGAN. So when you are referring to Darvon, it does not matter whether it has the T or the N to it?

Dr. MOERTEL. Provided they were used therapeutically in equivalent doses.

Senator MORGAN. 100 milligram napsylate is equivalent to 65 milligrams of the other, in other words?

Dr. MOERTEL. Yes.

In these studies I have shown the results of 10 studies in which combinations of Darvon plus over-the-counter drugs were compared to combinations of codeine or Talwin (pentazocine) plus over-the-counter drugs—8 of the 10 comparisons favored either the codeine or the Talwin combinations.

In short, the results of our Mayo Clinic studies are entirely consistent with preponderance of the studies done by other investigators.

It can be concluded that Darvon does have some pain relieving activity, but this is very minor and does not match up to the safer and readily available over-the-counter drugs.

Combinations of Darvon with aspirin, APAP or APC are not better than using the over-the-counter drugs alone.

If the patient requires more pain relief than over-the-counter drugs can provide, the physician should not prescribe Darvon compound or Darvocet-N because he has other more effective drug combinations available to him.

The only real difference between the Darvon compound and over-the-counter analgesics is the price. If you use 1978 Redbook average wholesale prices and add on a 30-percent markup for retail sales, the price for 100 tablets of Darvocet-N plus asprin is $11.50 and for 100 tablets of Darvon-N plus APAP is $13.50. If you are a careful shopper you can go to your corner drugstore or supermarket and get 100 two-tablet doses of APAP for about $2 or 100 two-tablet doses of aspirin for less than $1.

The case against Darvon would seem obvious. In the face of all this evidence, what arguments can be made in favor of Darvon.

There are three you will probably hear. The first is that the studies showing Darvon to have little or no value are not pertinent because they involved single doses of Darvon given as needed for pain. This argument is not credible. First, because there is no clinical evidence from well controlled studies to support it.

Also, the typical patient who may have a headache or a backache or pain after dental extraction doesn't want medication that he has to take regularly over a long period of time before it gives optimum relief.

He wants to take a single dose that will give him pain relief quickly.

Finally, the pharmaceutical manufacturer itself in its advertising to the physician and in its package insert, recommends that Darvon be taken as needed.

Another argument is that 65 milligrams of Darvon hydrochloride is about equal in effectiveness to 65 milligrams of codeine when both are given by mouth. Basically, I feel that is pretty close to true, but that is really a bit of smokescreen.

Sixty-five milligrams of codeine given alone by mouth is really not a very effective analgesic.

Given by a hypo, this dose is very effective. By mouth, however, it has been shown repeatedly to be no better than aspirin, and in our first study, although I did not display it on the graph, it was not quite as good.

Now, you can get effective pain relief by using codeine alone, by mouth, but when you use it by mouth, you have to use a much larger dose.

The important issue is whether these drugs add to the effectiveness of aspirin or APC, because that is the way they are both usually prescribed.

Here, when codeine is added, as in Empirin compound with codeine, you do get a significant improvement in analgesia. When Darvon is added, you do not.

Yet, another argument I am sure you will hear. For the past 20 years, Darvon has been prescribed by more doctors than any other prescription analgesic, and how could all these doctors be wrong.

Well, this contention really has a very hollow ring in the face of medical history. Over the centuries, it has at one time or another been the consensus of the most learned doctors that miraculous cures of almost all diseases could be obtained through the use of such things as mummy dust, unicorn's horn, poltices, purges, blood-letting, or even into this century, leeching.

I rather suspect this happened because some enterprising corporation cornered the market on leeches, and then proceeded to spend an enormous amount of money advertising them in the medical journals.

Within just the past 40 years, I am sure many of us here still remember the revered family physician with his black satchel filled with compartments containing innumerable bottles of medicines, and he would stake his reputation on each and every one of them.

Since then I would estimate at least 95 percent of these drugs have been shown to be without any value, and are no longer used.

It is only in very recent years that doctors have just begun to blend compassion for the sick with scientific method. I very much hope that you gentlemen will encourage this trend.

So to summarize. I will answer specifically the four questions addressed to me when I was invited to testify before this committee.

The first question, from my knowledge and experience what is the relative efficacy of Darvon as compared to other analgesics?

In my judgment Darvon is inferior to the commonly marketed aspirin, acetaminophen, or APC combinations.

The second question, is it possible to treat patients for pain with analgesics other than Darvon?

Absolutely.

For patients with mild pain you can do just as good a job, if not better, with aspirin or APAP alone, and you can do it at about one tenth of the price.

With regard to the use of Darvon combinations for the treatment of moderate pain, you can achieve significantly superior pain relief using combinations of aspirin with codeine, aspirin with oxycodone, or aspirin with pentazocine or Talwin.

For the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient.

The third question, is it possible to maintain good medical practice without the use of Darvon?

Yes.

I would seriously question whether the use of Darvon is good medical practice at all. And the last question, what is the medical justification for using Darvon?

I know of none.

Thank you.

Senator NELSON. Then I guess you answered the question I intended to ask. You say there is no justifiable reason for using Darvon.

I was going to ask if there has been isolated any special target group that benefits more from Darvon than from another analgesic, keeping in mind the estimate that about 5 percent of all patients are allergic to aspirin.

If that is the case, perhaps they should have acetaminophen, or if there is something wrong with that, codeine.

Have any scientific studies identified a target group of special beneficiaries for the use of Darvon?

Dr. MOERTEL. I think the important part of that question, and in answer to Senator Hayakawa's question is the last statement you made, that is, is there a group that has been identified by scientific study to be a target area, and the answer is simply that no specific group has been identified as such a target group.

Of course, there are people that claim I only get relief with Darvon. We had a number of these patients in our study, and when they did not know what they were taking, their strong beliefs were simply not so. Darvon has a great mystique about it, and when many of us take medications, this mystique is a very helpful therapeutic thing, but whether or not there is any pharmaceutical properties in Darvon that makes it particularly effective for a given group, there is no study to my knowledge that has ever demonstrated it.

Senator NELSON. Thank you very much for your very helpful testimony.

Any questions?

Senator MORGAN. No questions.

Mr. TWARDY. Just a simple question.

I notice the others on the panel have indicated they are representing their own views and not those of the institutions where they practice.

Are your views those of the Mayo Clinic or your own?

Dr. MOERTEL. I would only purport to present my personal views in this testimony.

I am not representing the Mayo Clinic or any statement other than my own.

Mr. TWARDY. You seem to have indicated the idea of a multidose study.

Was the cancer study which you conducted a single dose or a multidose study?

Dr. MOERTEL. That was a single-dose study.

Mr. TWARDY. Might the results have been different if it had been a multidose study?

Dr. MOERTEL. That is a very iffy question, and I would have to answer yes to any "might" question, but no, we did not demonstrate it.

Mr. TWARDY. So it is possible that if a multidose study had been made the patients would have experienced a more satisfactory result?

Dr. MOERTEL. I have never found it demonstrated that this is so, so as a physician and a scientist, I must question it, until somebody produces the information to prove it.

Senator NELSON. Thank you very much, Dr. Moertel.

Dr. MOERTEL. Thank you.

Senator NELSON. We have a paper that was written for the Journal of American Medical Association, by you, Dr. Moertel.

Do you wish to have that printed in the hearing record?

Dr. MOERTEL. Senator Nelson, I did not submit that reprint to you. I would be very pleased to have it printed though, if this is the desire of the committee.

Senator NELSON. It addresses itself to these studies.

The title is "Relief of Pain by Oral Medications, a Controlled Evaluation of Analgesic Combinations."

Dr. MOERTEL. This is undoubtedly a reprint of the second study of which I referred, but as I said, I did not provide that reprint to the committee.

Senator NELSON. We will review it, and if it adds to your testimony, we will simply print it in the record.

[The prepared statement and supplemental information of Dr. Moertel follows:]

TESTIMONY BEFORE THE SELECT COMMITTEE ON SMALL BUSINESS, U.S. SENATE, CHARLES G. MOERTEL, M.D., MAYO CLINIC, ROCHESTER, MINN.

Studies involving Darvon and its combinations conducted at the Mayo Clinic have primarily involved treatment of the patient with advanced cancer. For these patients our single most overriding responsibility is relief of pain. Unfortunately in this vital area we as physicians frequently perform rather poorly. In our medical schools instruction in the practical use of drugs is often inadequate. Our judgment in prescribing drugs for pain is quite comparable to the public's judgment in purchasing over the counter drugs for pain. Both are largely governed by advertising. We as doctors are no less vulnerable than the public at large to the persuasive influence of Madison Avenue. For vivid evidence of this you only have to look at the Physicians Desk Reference. This is a manual distributed free of charge to all physicians each year by the Pharmaceutical Manufacturers Association. It lists all prescription drugs promoted by pharmaceutical companies. In the 1978 edition there were 149 drugs advertised for relief of pain by oral route of administration.

More than a decade ago, because we were disturbed by our ineptitude in the management of pain of the cancer patient, we initiated at the Mayo Clinic carefully controlled research studies to evaluate the relative effectiveness of the many mdications for pain that were available to us. Our only vested interest was our patient in pain and these studies were not paid for by any drug company.

To insure that the results of these studies could not be in any way influenced by us or by any preconceived ideas of our patients, we double blinded the studies. By this I mean that all of the pain medications we gave to the patients looked exactly alike and were identified only by code number. Neither we nor the patients could tell which was which. The drugs were administered in randomized sequences and we only broke the code when the entire study was completed.

In our first study we looked at analgesic drugs in their pure form and this study compared nine different analgesics as well as placebo or sugar pill. It involved close to 600 drug evaluations. Our results with the four drugs that are pertinent to this hearing are displayed in Table 1. As in all studies, even with cancer pain, there will be a substantial number of patients who claim relief with sugar pills. Darvon showed some advantage over sugar pills, but this was small and not statistically significant—that is the difference could easily have occurred by accident. Acetaminophen or APAP—commonly marketed as Tylenol or Datril—showed a much more substantial degree of relief; and surprisingly, leading the pack, two simple aspirin tablets. The superiority of aspirin over Darvon was statistically significant—by that I mean that the odds are greater than 20 to 1 that this difference did not occur by chance alone. These results were quite startling to us because at that time Darvon led the market in prescription drug sales.

It can reasonably be argued that although interesting these results really aren't a fair evaluation of Darvon. Although Darvon is sold in pure form, it is usually marketed in combination with aspirin or APAP or with APC as the so-called Darvon compound. In a second study we, therefore, looked at aspirin alone compared to aspirin plus a variety of other drugs that are commonly marketed in aspirin containing drug combinations. This study involved 100 patients in 1000 separate drug evaluations. In Table 2 you can see that again

aspirin showed a significant advantage over placebo. The addition of a full dose of Darvon to aspirin, however, provided essentially no improvement in pain relief. You can also see that within this same study it was demonstrated that two prescription drugs did provide better relief than aspirin alone. These are the combinations of either Talwin (Pentazocine) or coedeine with aspirin. The time honored codeine—aspirin combination also showed a statistically significant advantage to the Darvon—aspirin combination—again the odds better than 20 to 1 that this difference did not occur by accident.

Based on our results we would have to conclude that if Darvon alone has any pain relieving effect, this is trivial and simply doesn't match up to common, inexpensive over-the-counter drugs. We must also conclude that the combination of Darvon with aspirin holds no advantage to aspirin alone, and if a patient requires a stronger analgesic the physician should prescribe some other more effective drug regimen.

These, however, are just the results from a single institution; and although we feel our studies were of sound design and conducted meticulously and analyzed without bias, it is possible that there could be some unrecognized distorting quirk in our methodology or that cancer pain is not representative of other types of pain. We only really feel comfortable with clinical experimental results when they are confirmed by others.

Over the remainder of my testimony I'd like to review all of the published medical literature of which I am aware that pertains to the clinical evaluation of Darvon as an analgesic agent. Here I'm only going to refer to the controlled, randomized, double-blind studies. When your endpoint of a study is as subjective as pain relief, these are the only kind of studies you can believe.

In all, we found 34 such studies involving various types of pain and these are listed in the bibliography which I have supplied. In Table 3 I've displayed the results of the 23 studies in which standard doses of Darvon alone were compared with placebo. You can see that none of the studies favored sugar pills. In four of the studies there was essentially no difference between Darvon and sugar pills. In seven the results favored Darvon but the difference was not statistically significant. Our first study is included in these. In 12 of the 20 studies Darvon was favored and the result were statistically significant. Based on these overall results it is reasonable to conclude that Darvon alone does have some analgesic activity although its not very striking. If, for example, aspirin alone had been tested in the 23 study populations of patients with relatively mild pain, it could be reasonably anticipated that aspirin would have been strongly favored in all 23.

In Table 4 I've displayed the results of 14 studies in which Darvon alone at standard doses was compared to common over the counter drugs—aspirin alone, acetaminophen or APAP alone, or APC. Among this group there were no studies favoring Darvon, in one study there was no difference, and in the remaining 13 of the 14 studies the over-the-counter drugs were favored over Darvon. In seven of these the differences were statistically significant.

In Table 5, I've shown the studies involving standard doses of Darvon in combination with aspirin, APAP, or APC compound. The results of these combinations are compared to the results of the over-the-counter drugs used alone without the addition of Darvon. Three studies favored Darvon combinations, three favored the over-the-counter drugs used alone, and 6 of the 12 studies showed no difference. It's of interest that there are two other studies of this kind that have not appeared in the medical literature although they have been highly publicized in lay media. It seems that some ad men at a proprietary pharmaceutical company must have been looking at the overall Darvon literature and decided they could make a real good sales pitch by showing their over-the-counter analgesic was just as good as Darvon compound. So they proceeded to contract out for two clinical research studies and that is exactly what the studies showed. Perhaps you remember the subsequent ads that appeared on the media displaying an Anacin tablet side by side with a Darvon compound capsule and accompanied by the advertising claim that Anacin had been shown in two medical studies to provide just as much relief as the high priced prescription item.

In Table 6 I've shown the results of ten studies in which combinations of Darvon plus over the counter drugs were compared to combinations of codeine or Talwin (pentazocine) plus over-the- counter drugs. Eight of the 10 comparisons favored either the codeine or the Talwin combinations.

In short, the results of our Mayo Clinic studies are entirely consistent with preponderance of the studies done by other investigators. It can be concluded that Darvon does have some pain relieving activity but this is very minor and

does not match up to the safer and readily available over the counter drugs. Combinations of Darvon with aspirin, APAP or APC are not better then using the over-the-counter drugs alone. If the patient requires more pain relief than over-the-counter drugs can provide, the physician should not prescribe Darvon compound or Darvocet N because he has other more effective drug combinations available to him. The only real difference between the Darvon combinations and over-the-counter analgesics is the price. If you use 1978 Redbook average wholesale prices and add on a 30% markup for retail sales, the price for 100 tablets of Darvocet N plus aspirin is $11.50 and for 100 tablets of Darvon N plus APAP is $13.50. If you are a careful shopper you can go to your corner drug store or supermarket and get 100 two tablet doses of APAP for about $2.00 or 100 two tablet doses of aspirin for less than $1.00.

To summarize, I will answer specifically the four questions addressed to me when I was invited to testify before this committee. The first question, from my knowledge and experience what is the relative efficacy of Darvon as compared to other analgesics? In my judgment Darvon is inferior to the commonly marketed aspirin, acetaminophen, or APC combinations. The second question, is it possible to treat patients for pain with analgesics other than Darvon? Absolutely. For patients with mild pain you can do just as good a job, if not better, with aspirin or APAP alone, and you can do it at about one tenth of the price. With regard to the use of Darvon combinations for the treatment of moderate pain, you can achieve significantly superior pain relief using combinations of aspirin with codeine, aspirin with oxycodone, or aspirin with pentazocine or Talwin. For the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient. The third question, is it possible to maintain good medical practice without the use of Darvon? Yes. I would seriously question whether the use of Darvon is good medical practice at all. And the last question, what is the medical justification for using Darvon? I know of none.

TABLE 1.—MAYO CLINIC EVALUATION OF ANALGESICS IN PURE FORM

Agent	Patients	Percent pain relief
Aspirin, 650 mg	57	62
Acetaminophen (APAP, 650 mg)	57	50
Darvon HCl, 65 mg	57	43
Placebo	57	32

Note: Aspirin superior to Darvon, $p<0.05$. Reference: 22.

TABLE 2.—MAYO CLINIC EVALUATION OF ANALGESIC COMBINATIONS

Regimen	Patients	Percent pain relief
Codeine, 65 mg plus ASA	100	55
Talwin, 25 mg plus ASA	100	54
Darvon N, 100 mg plus ASA	100	41
Aspirin alone, 650 mg (ASA)	100	39
Placebo	100	23

Note: Codeine plus ASA superior to aspirin alone and to Darvon plus ASA, $p<0.05$. Reference: 23.

TABLE 3.—PUBLISHED COMPARISONS OF DARVON[1] WITH PLACEBO

Study result	Number of studies
Strongly favoring Darvon	12
Favoring Darvon	7
No difference	4
Favoring placebo	0
Strongly favoring placebo	0

[1] Darvon at standard doses. Darvon HCl 32.5 to 65 mg; Darvon N 100 mg.

References: 1,4,5,6,7,9,10,11,12,13,15,16,18,23,26,28,31,32,33,34.

TABLE 4.—PUBLISHED COMPARISONS OF DARVON WITH OVER-THE-COUNTER (OTC) ANALGESICS (ASPIRIN, ACETAMINOPHEN (APAP), OR APC)

Study result	Number of studies
Strongly favoring Darvon	0
Favoring Darvon	0
No difference	1
Favoring OTC drugs	6
Strongly favoring OTC drugs	7

References: 5,12,13,15,16,19,20,21,23,26,29,33.

TABLE 5.—PUBLISHED COMPARISONS OF DARVON PLUS OTC DRUGS (ASPIRIN, APAP, APC) VERSUS OTC DRUGS USED ALONE

Study result	Number of studies
Strongly favoring Darvon plus OTC	2
Favoring Darvon plus OTC	1
No difference	6
Favoring OTC alone	2
Strongly favoring OTC alone	1

References: 2,3,10,11,12,17,18,19,22,24,26,28.

TABLE 6.—PUBLISHED COMPARISONS OF DARVON PLUS OTC DRUGS VERSUS CODEINE OR TALWIN PLUS OTC DRUGS

Study result	Number of studies
Strongly favoring Darvon plus OTC	0
Favoring Darvon plus OTC	0
No difference	2
Favoring codeine or Talwin plus OTC	4
Strongly favoring codeine or Talwin plus OTC	4

References: 5,6,10,12,22,23,25,26,27.

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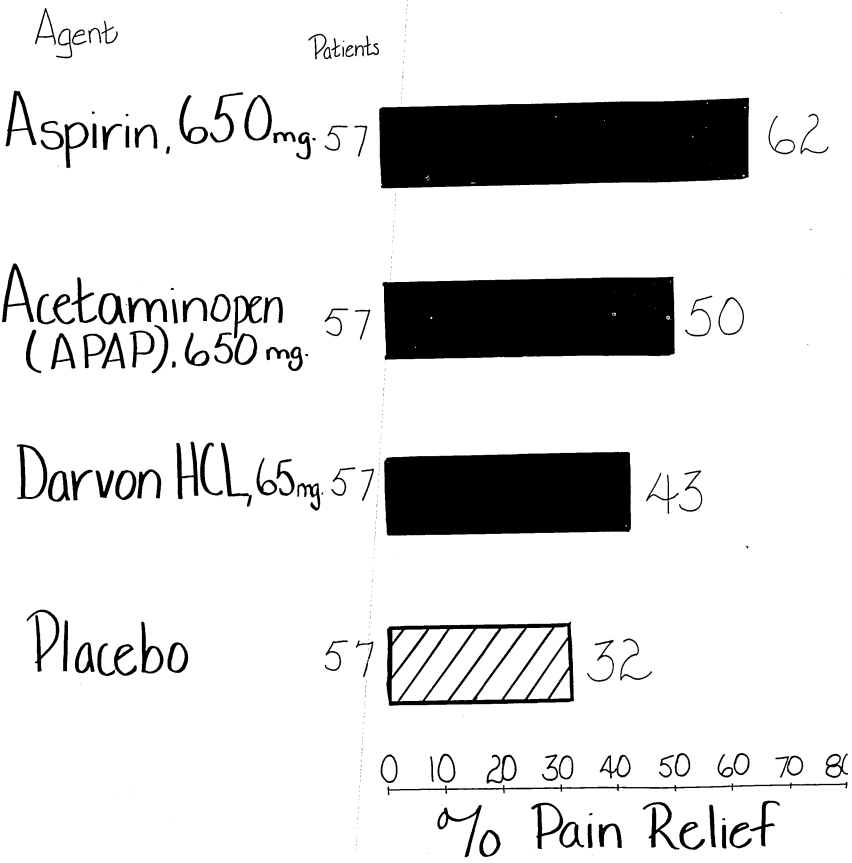
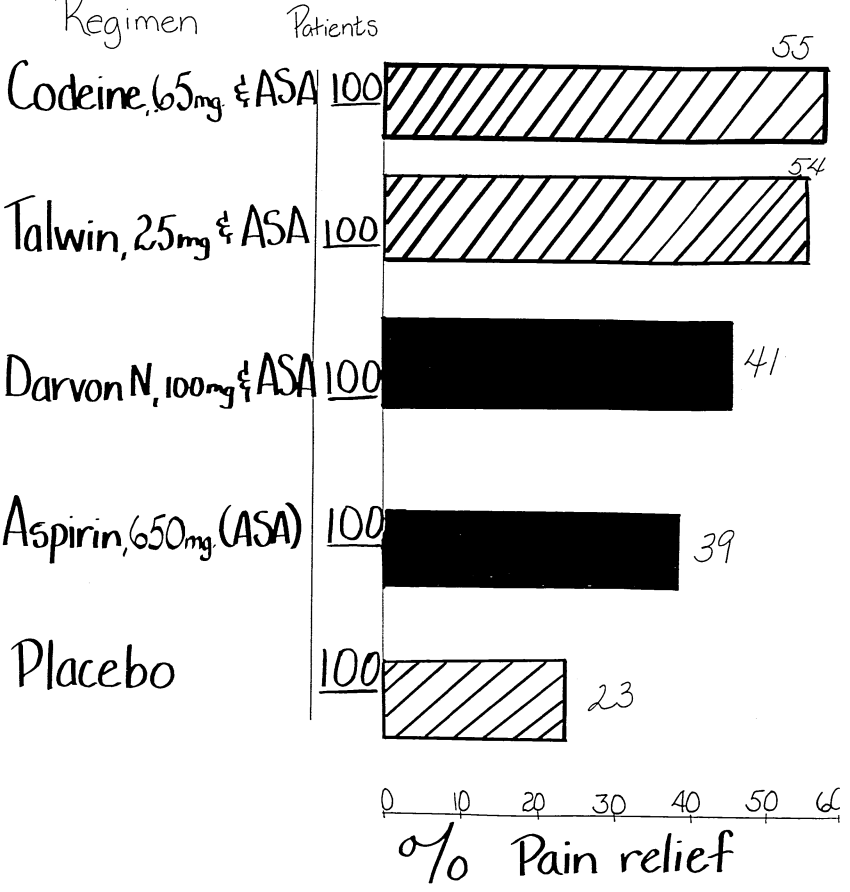
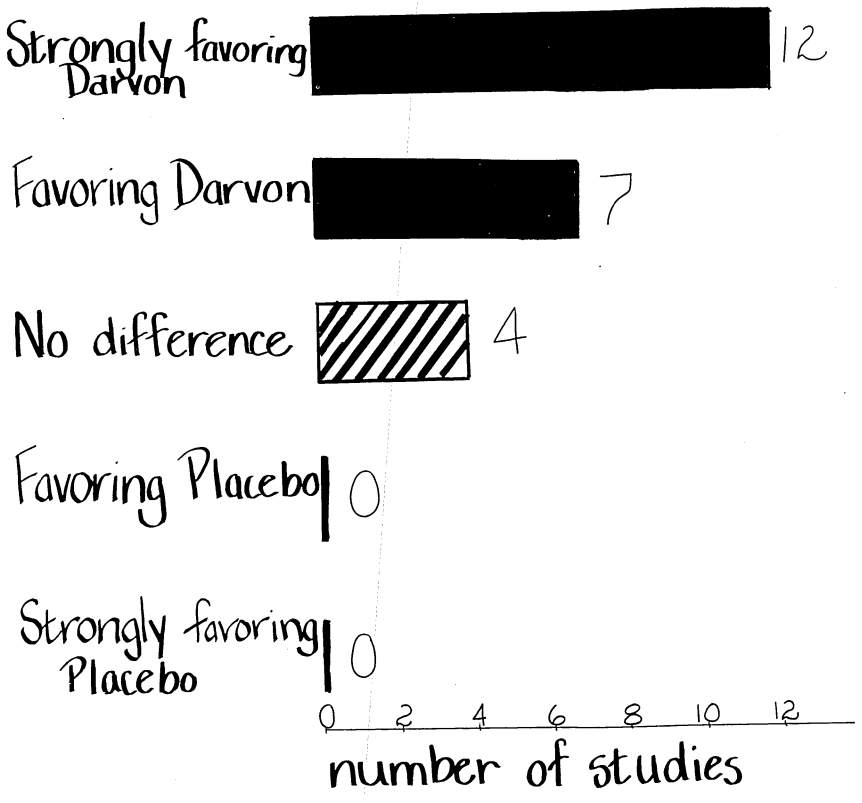
Mayo Clinic Evaluation of Analgesics in Pure Form

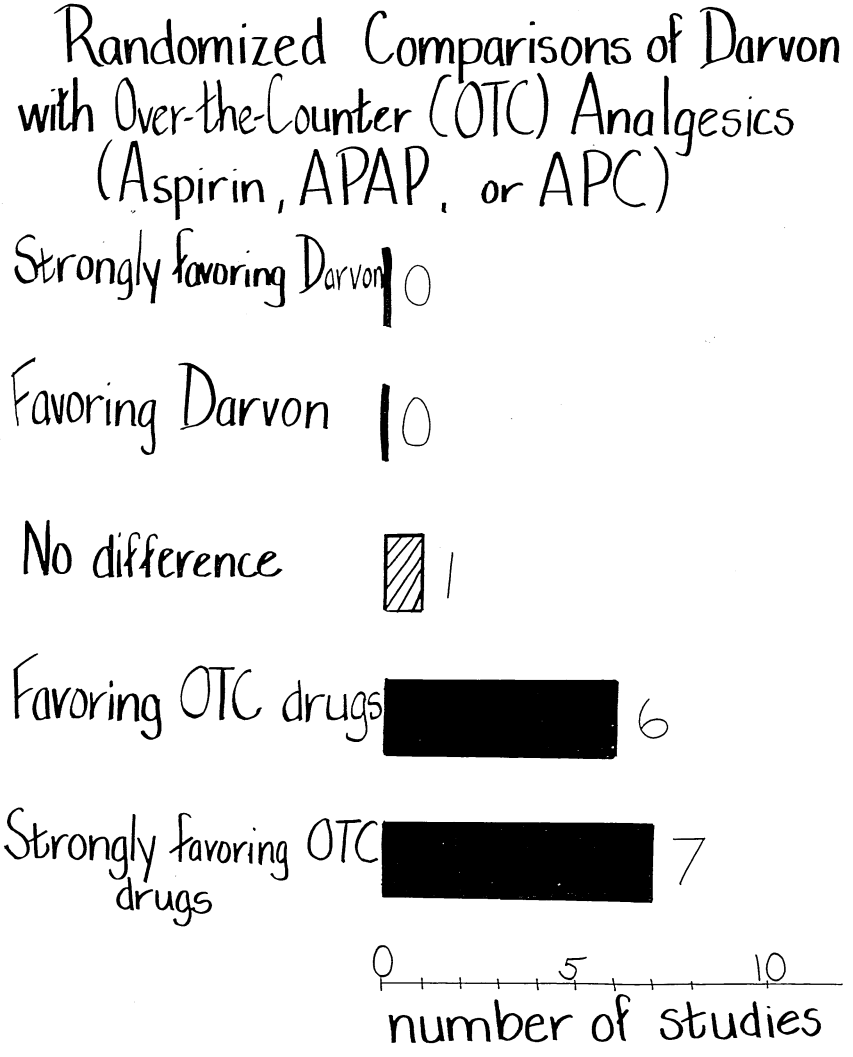


Mayo Clinic Evaluation of Analgesic Combinations



Randomized Comparisons of Darvon with Placebo




Randomized Comparisons of Darvon with Over-the-Counter (OTC) Analgesics (Aspirin, APAP, or APC)
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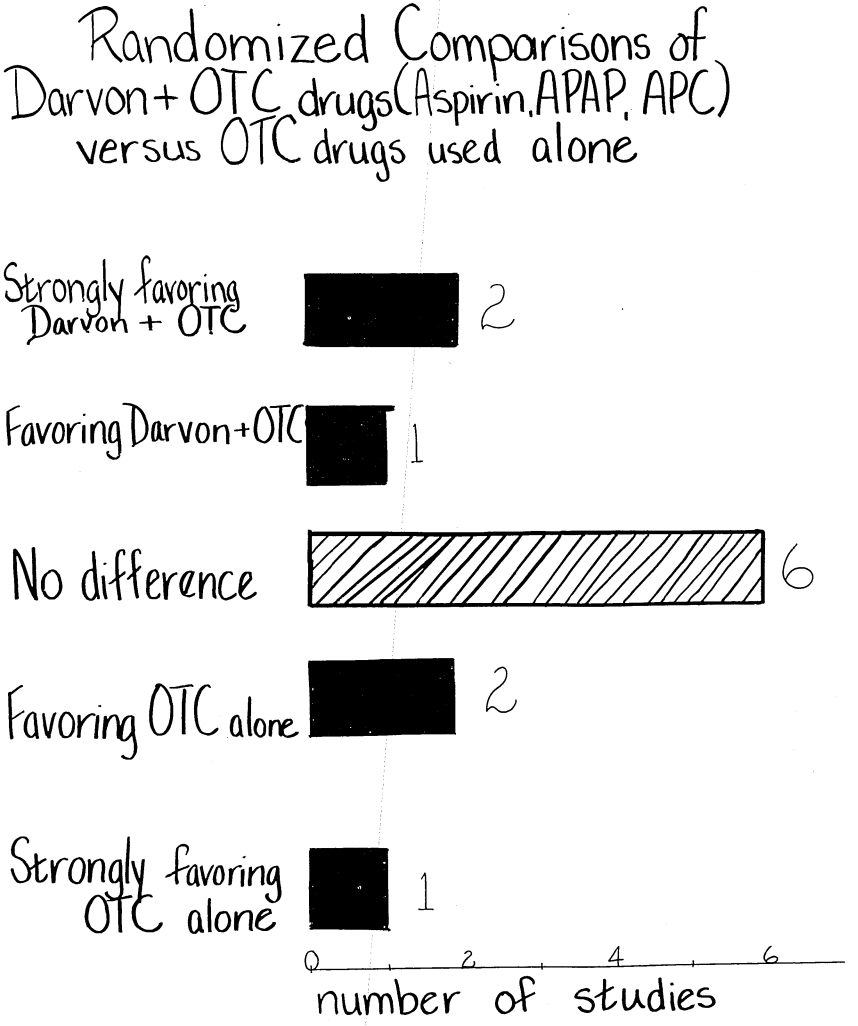
0
Favoring Darvon
0
No difference
1
Favoring OTC drugs
6
Strongly favoring OTC drugs
7
0
5
10
number of studies


Randomized Comparisons of
Darvon + OTC drugs (Aspirin, APAP, APC)
versus OTC drugs used alone
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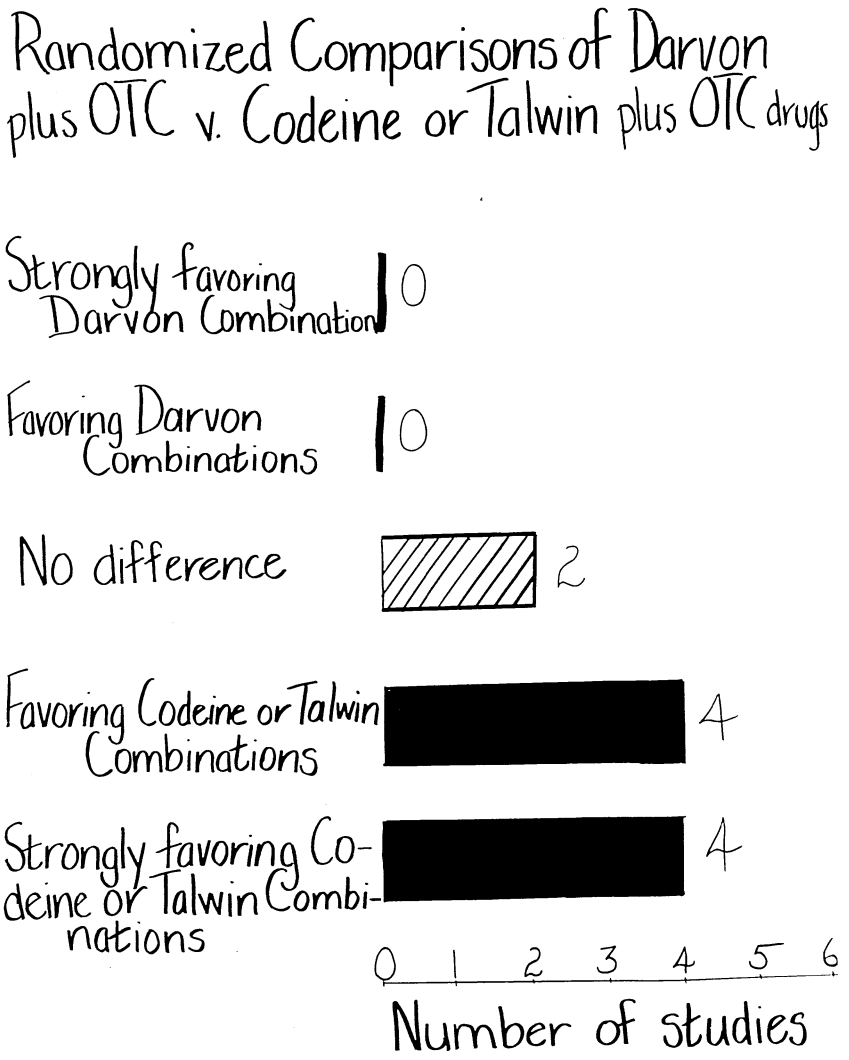
Favoring Darvon + OTC
1
No difference
6
Favoring OTC alone
2
Strongly favoring OTC alone
1
0
2
4
6
number of studies


Randomized Comparisons of Darvon plus OTC v. Codeine or Talwin plus OTC drugs
Strongly favoring Darvon Combination
0
Favoring Darvon Combinations
0
No difference
2
Favoring Codeine or Talwin Combinations
4
Strongly favoring Codeine or Talwin Combinations
4
0 1 2 3 4 5 6
Number of studies

Relief of Pain by Oral Medications

A Controlled Evaluation of Analgesic Combinations

Charles G. Moertel, MD; David L. Ahmann, MD; William F. Taylor, PhD; Neal Schwartau

• **A double-blind study of analgesic drug combinations was conducted, involving 100 patients with pain due to cancer. The combinations of 650 mg of aspirin plus either 65 mg of codeine, 9.76 mg of oxycodone, or 25 mg of pentazocine hydrochloride each produced significantly greater pain relief than aspirin alone. Side effects for a single dose of these effective combinations were essentially equal and clinically tolerable. The combinations of 650 mg of aspirin plus either 65 mg of caffeine, 32 mg of pentobarbital sodium, 25 mg of promazine hydrochloride, 75 mg of ethoheptazine citrate, or 100 mg of propoxyphene napsylate did not show significant advantage in analgesic effect over aspirin alone.**

(*JAMA* 229:55-59, 1974)

BY FAR the most common pharmacologic challenge encountered by the physician today is relief of pain. The demand for oral analgesics dominates both the prescription and nonprescription drug markets. The *1973 Physicians' Desk Reference* lists 113 different brand-name drugs promoted for pain relief by oral administration; to this list must be added perhaps an even larger number of nonpromoted, generic prescription drugs and heavily promoted over-the-counter preparations.

Although several analgesics and narcotics have been demonstrated to produce significant relief of pain when given alone, the modern trend among pharmaceutical industry, physician, and patient seems clearly to be in favor of analgesic combinations. Of oral analgesics listed in the *Physicians' Desk Reference*, 83% are combinations. The largest-selling prescription drug in this country, Darvon Compound-65, and the two largest-selling brand name over-the-counter drugs, Anacin and Excedrin, are all combination analgesic drugs. Whether this great popularity of analgesic drug combinations is the result of true therapeutic superiority or superiority in promotional efforts becomes a difficult point to resolve on the basis of scientific evidence. Although the need for well-designed programs of clinical evaluation of analgesic drug combinations is great, investigators have seemed reluctant to enter this sensitive arena, and controlled trials of analgesic combinations have been recorded only infrequently in the literature.

In a previous double-blind evaluation of single analgesics,[1] we found aspirin at a dosage of 650 mg to be significantly superior to placebo and to be unexcelled in analgesic effect by any of the other single-entity medications we tested at manufacturers' recommended dosages.

Aspirin also has proved to have consistent analgesic activity in controlled studies conducted by numerous other investigators,[2] and 650 mg probably approximates the ideal dosage. The purpose of this study was to compare the analgesic effectiveness of 650 mg of aspirin used alone with the analgesic effectiveness of the same dose of aspirin in combination with other drugs of the type commonly incorporated into marketed analgesic combinations.

Materials and Methods

One hundred patients were chosen for study, each of whom had chronic or recurring pain problems resulting from unresectable cancer. All were ambulatory outpatients, and all could reliably tolerate oral medications. The patients did not have appreciable systemic symptoms related to their malignant disease, and they were not receiving any antitumor treatment (eg, chemotherapy or radiation therapy) that could confuse observation of analgesic side effects. The pain that the patients experienced was assumed to be related to intra-abdominal, retroperitoneal, pelvic, or osseous malignant tumors. The degree of pain was classified as mild or moderate. Patients were excluded from study if they gave a history of an allergic reaction to any of the studied drugs. Patients also were not accepted for study if they had previously been on a schedule of narcotic drugs that was judged capable of producing any degree of physiologic dependence. Particularly, patients were chosen who in our opinion were intelligent, dependable observers. They were informed they were participating in a randomized type of study. Patients were not allowed any other analgesics, narcotics, sedatives, stimulants, anti-

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emetics, antidepressants, tranquilizers, or alcoholic beverages during the study.

The following single agents and drug combinations were evaluated in each patient: placebo, 650 mg of aspirin, 65 mg of caffeine plus 650 mg of aspirin, 32 mg of pentobarbital sodium plus 650 mg of aspirin, 25 mg of promazine hydrochloride plus 650 mg of aspirin, 75 mg of ethoheptazine citrate plus 650 mg of aspirin, 100 mg of propoxyphene napsylate plus 650 mg of aspirin, 75 mg of ethoheptazine citrate plus 650 mg of aspirin, 100 mg of propoxyphene napsylate plus 650 mg of aspirin, 25 mg of pentazocine hydrochloride plus 650 mg of aspirin, 9.76 mg of oxydone plus 650 mg of aspirin, and 65 mg of codeine sulfate plus 650 mg of aspirin. Oxycodone is not marketed and was not available to us in pure form. We therefore employed the marketed Nucodan which contains oxycodone salts plus a minute amount of homatropine terephthalate and a small dose of an analeptic drug, pentylenetetrazol.

put in separate envelopes. To prevent any degradation resulting from interaction between drugs during storage, aspirin and the other component of the combination were always delivered in separate capsules, not mixed in the same capsules. Regular commercial forms of each study drug were used. Lactose (USP) was employed as a placebo and also as a filler for all study drugs. Each patient was given a single dose of each of the study preparations and placebo in randomized sequences according to the latin-square method (10 such latin squares, each 10×10 in size). One drug preparation was directly followed by another, and there was no planned placebo or no-treatment interval between active drugs. Each patient received only one test sequence of each of the study preparations.

Patients were instructed to take the planned single dose whenever they felt definite pain, but no more often than every six hours. The intervals between doses were variable, therefore, depending on the requirement of the patient for analgesia, but none were shorter than six hours. A corresponding variability occurred in the total period required for each patient study (median time for completion, five days; mean, nine days). In essence, this study was designed to reproduce the conditions under which a physician prescribes an analgesic with the direction that it be used every six hours as needed for pain.

With each dose, patients were asked to record the time of administration, the time when the onset of definite pain relief was noted, and the time when pain returned. They were also asked to record what percentage of their initial pain was gone at the time when they obtained maximum relief from the medication. Specific inquiry was made regarding the following side effects: upset stomach, nausea, vomiting, sleepiness, dizziness, impaired thinking, and excitement. Patients were also asked to mention any additional side effects they may have experienced. This information was recorded on a separate form for each drug dose.

It should be emphasized that these observations were recorded by the patient himself immediately after each drug-dose experience. They were not recorded or interpreted by a medical observer. It should also be emphasized that this was a study only of single-dose administration, not of prolonged administration.

Statistical analysis was done in stages. First, the possible effects of sequence of drug administration were evaluated. These proved to be negligible and, consequently, the data were reanalyzed ignoring sequence effect. Significance testing of differences of pairs of drugs, after overall

Table 1.—Comparative Therapeutic Effect of Analgesic Preparations As Reported by 100 Patients

Analgesic Preparation	Mean Percent Pain Relief*†	Rank Sum*‡
Codeine sulfate, 65 mg+aspirin, 650 mg	63(S)	429(S)
Oxycodone, 9.76 mg+aspirin, 650 mg	63(S)	430(S)
Pentazocine hydrochloride, 25 mg+aspirin, 650 mg	59(S)	490(B)
Propoxyphene napsylate, 100 mg+aspirin, 650 mg	55(NS)	511(NS)
Promazine hydrochloride, 25 mg+aspirin, 650 mg	51(NS)	556(NS)
Pentobarbital sodium, 32 mg+aspirin, 650 mg	50(NS)	581(NS)
Caffeine, 65 mg+aspirin, 650 mg	48(NS)	603(NS)
Ethoheptazine citrate, 75 mg+aspirin, 650 mg	48(NS)	619(NS)
Aspirin, 650 mg	51(NS)	554(NS)
Placebo	33(I)	726(I)

*Letters in parentheses indicate significance: S, significant superiority to aspirin alone ($P<.05$); B, borderline superiority to aspirin alone ($P\approx.05$); NS, no significant difference from aspirin alone; I, significant inferiority to all other preparations ($P<.05$).

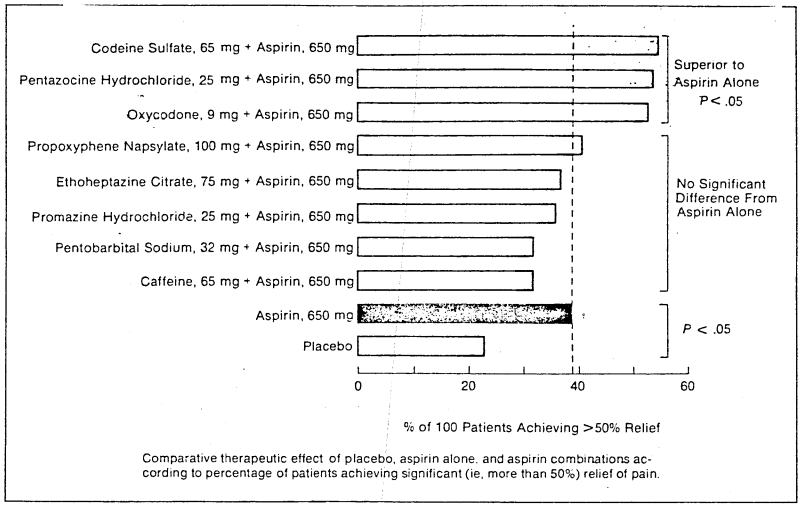
†Least significant difference for superiority ($P=.05$) is 6.2, on the basis of a one-sided test for superiority of a preparation when compared to aspirin.

‡Least significant difference for superiority ($P=.05$) is 61.8, on the basis of a one-sided test for superiority of a preparation when compared to aspirin.

Table 2.—Sedative Effect of Analgesic Preparations Among 100 Patients

Analgesic Preparation	% of Patients
Promazine hydrochloride, 25 mg+aspirin, 650 mg	40*
Pentobarbital sodium, 32 mg+aspirin, 650 mg	27*
Oxycodone, 9.76 mg+aspirin, 650 mg	24
Pentazocine hydrochloride, 25 mg+aspirin, 650 mg	21
Codeine sulfate, 65 mg+aspirin, 650 mg	20
Propoxyphene napsylate, 100 mg+aspirin, 650 mg	18
Ethoheptazine citrate, 75 mg+aspirin, 650 mg	16
Caffeine, 65 mg+aspirin, 650 mg	14
Aspirin, 650 mg	11
Placebo	13

*Significant increase in sedation over placebo ($P<.05$).



Comparative therapeutic effect of placebo, aspirin alone, and aspirin combinations according to percentage of patients achieving significant (ie, more than 50%) relief of pain.

significance was confirmed, was done by the Fisher least-significant-difference method.

Results

To avoid any possible distortion and to make full use of data, analgesic effects were evaluated in three ways.

First to be studied was the proportion of patients who claimed greater than 50% pain relief at any time during the six hours following drug administration. This approach seemed to be best in selection of patients who obtained a truly useful therapeutic effect. The results (Figure) indicated that aspirin alone had a significant advantage in analgesic effect over placebo. The combinations of aspirin plus either caffeine, pentobarbital, promazine, ethoheptazine, or propoxyphene were not significantly superior to aspirin alone. The combinations of aspirin plus either codeine, oxycodone, or pentazocine were essentially equal in their significant superiority to aspirin alone as well as to each of the other aspirin combinations.

The second means of analysis (Table 1) employed the mean percentage of analgesia achieved by each of the ten drugs as described by each patient. This method allows a relative crediting of all the degrees of analgesic effect varying from none to complete relief of pain. Again, aspirin is significantly superior to placebo; again, the combinations of aspirin plus either caffeine, pentobarbital, promazine, ethoheptazine, or propoxyphene showed no significant superiority to aspirin; and again, aspirin plus either codeine, oxycodone, or pentazocine are significantly superior to aspirin alone. By this means of analysis, aspirin plus propoxyphene assumes an equivocal position, ranking above aspirin alone but not at statistically significant levels, and ranking significantly below aspirin plus codeine or oxycodone but not significantly below aspirin plus pentazocine.

The third method of analysis (Table 1), perhaps the most important one from a comparative standpoint, employs the relative ranking of analgesic effect assigned by each patient to each of the test drugs or combinations, ie, the drug to which an individual patient attributed the greatest percentage of relief of pain was given the rank of one, the lowest percentage of pain relief a rank of ten. Ties were broken on the basis of duration of relief of pain. The figures recorded in Table 1 are the sums of ranks accorded each drug (or combination) by the 100 patients. All of the study preparations demonstrate a significant advantage over placebo. Still, aspirin plus either codeine, oxycodone, or pentazocine are the leaders with a significant advantage over aspirin alone. Again, aspirin plus propoxyphene is in fourth position, significantly inferior to aspirin plus either codeine or oxycodone, but not significantly different from aspirin alone. Analgesic ranks of each of the other combinations are approximately that of aspirin.

For none of the three methods of analysis did the order in which the drug preparations were given have a detectable influence on the grade of therapeutic effectiveness accorded any single drug. The latin-square design of this study permitted a careful analysis which led to this finding.

No practical advantage was found for any of the study drug preparations with regard to the median time elapsed from ingestion to onset of definite pain relief. This ranged from

45 to 60 minutes (50 minutes for aspirin alone). Also, no practical difference was found in the median duration of pain relief that ranged between four and six hours (five hours for aspirin alone).

Except for sedation, all of the side effects for which we made specific inquiry or which the patients volunteered occurred at a frequency nearly equal for all ten drugs. The barbiturate sedative, pentobarbital, and the phenothiazine tranquilizer, promazine, produced a significant increase in sedation over the placebo (Table 2). The codeine, oxycodone, pentazocine, and propoxyphene combinations also produced increases in sedative effect when compared to placebo or aspirin alone, but these were not at a statistically significant level.

Comment

The problem of evaluating the effectiveness of analgesic combinations is made very complex by the fact that essentially all marketed products of this kind contain one or more of the analgesic-antipyretic type drugs, ie, aspirin, acetaminophen, or phenacetin. Since each of these drugs has well-established analgesic activity, the question is not whether the combinations will relieve pain; it is assumed that they will. The primary question is whether the addition of sedatives, stimulants, tranquilizers, or other analgesic agents of less well-established effectiveness really adds anything of value for the patient. Do these additives actually increase pain relief, or do they simply provide a vehicle for sales promotion and in the process subject the patient to increased cost, increased side effects, and increased risk of drug sensitization reactions?

Analgesic Combinations of No Significant Value.—As in our previous study,[1] aspirin again demonstrated a significant advantage in pain relief over placebo. The addition of the amount of caffeine equivalent to that in about one-half cup of coffee clearly added nothing to analgesic activity. A number of controlled evaluations of caffeine plus aspirin and phenacetin (APC) have also shown no superiority of this combination to aspirin alone for the relief of headache, postpartum pain, and acute and chronic pain problems of varying etiologies.[2]

Thirty-two milligrams of caffeine plus 400 mg of aspirin is the Anacin formula. Over-the-counter products such as Excedrin, Vanquish, Empirin compound, and APC compounds are mixtures of caffeine plus a lesser dose of aspirin (195 to 227 mg) with the deficit in aspirin made up by the addition of other analgesic-antipyretics such as phenacetin, acteminophen, or salicylamide. Although each of these preparations is several times as expensive as generic aspirin, there is no acceptable evidence that any provides the patient with more effective pain therapy. The widespread popularity of these preparations is clearly a tribute to the effective techniques of Madison Avenue.

The appealing presumption that allaying anxiety and apprehension will blunt pain perception has led to the marketing of a variety of combination analgesic preparations containing barbiturates or tranquilizers such as Darvo-tran, Equagesic, Fiorinal, Phenaphen, and Tranco-gesic. No evidence, however, supports this concept, and the work of Dundee and Moore[4] has seriously challenged it. In our study, the barbiturate and the tranquilizer produced the expected side effect of sedation, but they added nothing to analgesic effect. Certainly, if a patient presents a valid clinical indication for sedatives or tranquilizers, they should be employed, but for their own sake, not with the idea that they will contribute to pain relief. In view of the many potential hazards associated with indiscriminate use of barbiturates and tranquilizers, the marketing of such drugs in combination products directed primarily towards analgesia must be seriously questioned.

In our earlier study, ethoheptazine was essentially identical to placebo in analgesic effect.[1] In the present study, its combination with aspirin produces an identical analgesic effect to aspirin alone. There seems to be no valid indication for prescribing this agent either alone as Zactane, in combination with aspirin as Zactirin, or in combination with aspirin and meprobamate as Equagesic.

Propoxyphene hydrochloride used alone in our initial study showed a slight but insignificant advantage over placebo, and it was significantly inferior to aspirin.[1] Propoxyphene napsylate (Darvon-N) has been introduced as a drug that has the same analgesic effect as the hydrochloride form but allows more stable tablet formulation with aspirin. In this study, the propoxyphene napsylate combination was ranked higher than aspirin alone by all means of analysis, but in no instance was the difference statistically significant. It consistently ranked lower than codeine plus aspirin, and by all three methods of analysis, this difference was statistically significant. Thus, the therapeutic value of propoxyphene remains equivocal. The conflicting evidence in the literature regarding the effectiveness of propoxyphene, both alone and in combination, has been extensively reviewed by Beaver[5] and by Miller and associates.[6] Unquestionably, propoxyphene and its combinations are exceedingly popular prescription items, but it remains to be clearly established that this popularity reflects true analgesic effectiveness.

Effective Analgesic Combinations.—Three combinations—aspirin plus 65 mg of codeine, aspirin plus 9.76 mg of oxycodone, and aspirin plus 25 mg of pentazocine hydrochloride—showed a significant superiority in analgesic effect over simple aspirin and over all the other combinations tested. Codeine and pentazocine hydrochloride when used alone had shown a significant superiority over placebo in our earlier study.[1] The side effects of these three combinations were equally tolerable in the present single-dose study. It should be emphasized, however, that we employed only a 25-mg dose of pentazocine hydrochloride compared to the marketed form containing 50 mg. In our earlier study, we had found the 50-mg dose of pentazocine hydrochloride to produce sufficient gastrointestinal and central-nervous-system side effects to limit seriously its usefulness for the ambulatory outpatient. Oxycodone presents the very distressing hazard of increased addiction potential when compared to other available oral agents used for relief of mild to moderate pain. The serious addiction problems that may be associated with oxycodone were stressed ten years ago in the comprehensive review of Bloomquist.[7] He presented evidence that addiction liability was at least

comparable to that of morphine, and he concluded that increased misuse of oxycodone-containing drugs had caused the addiction of numerous persons not associated with the illicit drug trade. Since then the oxycodone-containing drugs (eg, Percodan) have been reclassified under the narcotic control laws. In view of the essentially equal analgesic and single-dose side effects when compared to codeine, there would seem to be little reason for the physician to subject his patient to the increased addiction hazard of the oxycodone analogue.

Another major difference between these three effective analgesic combinations is cost. On the basis of the average cost among a hospital pharmacy, a medical-center pharmacy, a chain-store pharmacy, and a privately owned neighborhood pharmacy in Rochester, Minn, on July 11, 1973, one hundred doses of oxycodone (9.76 mg) plus aspirin (200 Percodan tablets) will cost the patient $18.12. One hundred doses of codeine sulfate (65 mg) plus aspirin will cost $10.61. Pentazocine is not marketed in combination with aspirin, and to obtain the combination tested in this study, the patient must break a 50-mg pentazocine (Talwin) hydrochloride tablet in half and take aspirin separately. It would seem worth the nuisance, however, since 100 doses of 25 mg of pentazocine hydrochloride (50 Talwin hydrochloride tablets) cost only $4.95.

Study Methodology: Strengths and Limitations.—The methodology of this study was purposefully designed to approximate closely the conditions that exist when the physician prescribes an analgesic for an ambulatory patient with a pain problem. The patient went about his usual life activities during this study, and the patient himself selected the time when he felt an analgesic was required. By this means, the therapeutic procedure was tested in the same setting in which it would be applied clinically. Also, the subjective result was recorded directly by the patient without the possible distortion that could be introduced by a physician, nurse, or technician interviewer. Although this method has obvious advantages, it also has some very definite limitations. Accuracy of results is dependent on the reliability of the patient in following instructions and upon his ability to record observations clearly.

Innumerable uncontrolled variables may and frequently do influence the patient's response to each of the individual drugs studied. These include changes in his emotional status, whether he is rested or fatigued, the many and varied environmental stresses to which he may be subjected, whether the drug is taken in a fasting state or on a full stomach, whether the patient is active or at rest after taking the medication, and others. If, however, the experimental system is sensitive and of rational design, these uncontrolled variables should distribute themselves with reasonable uniformity throughout the population studied, so that statistical analysis will recognize differences in therapeutic effect if they exist. In this study, there were built-in quality controls of sensitivity provided by known differences between the drug preparations that should be detectable. Aspirin has an analgesic activity established by numerous investigators, and in this study aspirin was significantly superior to placebo by all means of statistical analysis. In addition, both pentobarbital and promazine have a well-established sedative activity, and in this study both showed a statistically significant increase in sedative activity in comparison to placebo. On the basis of this evidence, we feel justified in presuming that our study design is adequate to detect both analgesic activity and side effects under conditions closely simulating the circumstance when an oral analgesic preparation is prescribed in clinical practice. We must emphasize, however, that our results can be strictly applied only to the patient population and methods we employed. They cannot be interpreted as representative of the analgesic response that may be obtained for pain problems of different etiology, nor can they be assumed to have any direct application to the long-term response to analgesic agents.

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Senator NELSON. Our next witness is Dr. Page Hudson, chief medical examiner of the State of North Carolina.

STATEMENT OF PAGE HUDSON, M.D., CHIEF MEDICAL EXAMINER OF THE STATE OF NORTH CAROLINA

Dr. HUDSON. Thank you, Mr. Chairman.

Senator MORGAN. Before Dr. Hudson begins, I might say that Dr. Hudson is a very noted, highly respected member of the medical profession in North Carolina.

He and I worked together many years ago when I was attorney general, and he became chief medical examiner.

Senator NELSON. Let me say the witnesses were invited today because of their national distinction, and we are delighted to have you here.

Dr. HUDSON. Senator Nelson, members of the committee, I am very grateful for the opportunity to speak.

Unless requested specifically, I would prefer to not go into my entire statement.

Senator NELSON. Your statement will be printed in full in the record. It is always helpful to the hearing process, after you get to about the third witness, if you can skip anything that might be particularly repetitious. But you may present it however you desire.

Dr. HUDSON. Thank you.

My statement speaks to some material that has already been covered, so I would tend to skip that.

My particular area in medicine is what is called forensic pathology, which is that medical specialty that involves the detection, identification, and investigation and other studies of real or suspected unnatural deaths, and I practice and write and teach in this field of medicine and related sciences, and I have had the pleasure of serving as chief medical examiner of the State of North Carolina.

I will address myself to the experiences in that State.

Several years ago it became apparent to my colleague, Dr. Arthur J. McBay, who is here, who is chief toxicologist with the office of chief medical examiner, and to me that propoxyphene was responsible for an increasing number of deaths in our State.

We examined rather carefully our cases and our criteria, we have conferred with authorities in other States and with many physicians in our State, particularly physicians involved with daily patient care.

We began to get the feeling that we were into something that was awesome, at least to us, and that is that a drug medication appeared to exist, did exist, that was at the top in prescription popularity, one that had but a trace of benefit and that was reaching the point of causing more deaths than any drug, licit or illicit.

We saw the numbers of deaths from propoxyphene increase from just an occasional case in the late 1960's, or early 1970's, to 20 or so a year, a peak of 50 in 1975, and 40 or so the following year and 30 in subsequent years, and it was the drug causing the greatest number of deaths.

For the past 2 or 3 years, the deaths due to propoxyphene have been approximately twice that of the barbituates collectively.

We believe that most of these in our State have been suicide, in the area of two-thirds or three-quarters of them.

Some of course are very difficult to distinguish between suicide and accident.

We published some of our data and concerns in a letter to the Journal of American Medical Association in September 1975, and after assessing our data, we published an article about propoxyphene in the Southern Medical Journal in August 1975, and I think copies of these have been made available to you.

[The information follows:]

Letters

Letters, if clearly marked "For Publication," will be published as space permits and at the discretion of the editor. They should be typewritten triple-spaced, with five or fewer references, should not exceed two pages in length, and will be subject to editing. Letters are not acknowledged.

Propoxyphene Overdose Deaths

To the Editor.—We are observing an alarming increase in North Carolina in the number of deaths attributable to propoxyphene. We doubt that the phenomenon is peculiar to this state. Most physicians may not be aware of the problem, in spite of the article in THE JOURNAL by Sturner and Garriott (223:1125, 1973).

This state's Medical Examiner System detected 21 deaths in 1972 and 21 in 1973 attributable to propoxyphene. Thirteen such deaths were identified in the first half of 1974, and 17 more in the last half of that year. In the first three months of 1975, sixteen more deaths have been recorded. In comparison, there has been an average of 39 barbiturate deaths annually from 1971 to 1974. There have been only three barbiturate deaths during the first quarter of this year, when there were 16 propoxyphene deaths. Most of the propoxyphene deaths have been suicidal overdoses; some have been accidents.

Propoxyphene is a prescription analgesic second only to aspirin in popularity. The drug in the various forms of Darvon was the most commonly prescribed drug in 1972. Although Darvon is the most widely used propoxyphene, it is also available as Dolene, Pro-Gesic-65, and SK-65. The relatively new napsylate salt of propoxyphene, Darvon-N, is reputed to be safer than hydrochloride salt because of its poor solubility. We are unaware that one form of propoxyphene is demonstrably safer than another.

We offer several possibilities to account for the increase in recognized propoxyphene deaths: (1) the rescheduling-induced decrease in availability of rapid-acting barbiturates, (2) stricter controls on the much less lethal analgesic codeine; (3) the misconception among many physicians that propoxyphene is essentially harmless; and (4) the situation that Medicare will pay for propoxyphene prescriptions but will not pay for aspirin.

Communities that are not detecting propoxyphene deaths may not have adequate death investigative systems including competent toxicology facilities. Recent improvement in techniques may account for discovery of cases that would otherwise have gone undetected.[1] It is our opinion that 15 to 20 of the 65-mg capsules (or of the 100-mg napsylate salt compressed tablets) may cause death, and that somewhat lesser amounts may do so with ethanol or other central nervous system depressants. In our experience, blood concentrations of propoxyphene together with other depressants that exceed 0.1 mg/100 ml, and of propoxyphene alone that exceed 0.2 mg/100 ml, can cause death.

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1. McBay AJ, Turk EF, Corbett BW, et al: Determination of propoxyphene in biological materials. *J Forensic Sci* 19:81-89, 1974.

Edited by John D. Archer, MD, Senior Editor

Fatal Poisoning With Propoxyphene: Report From 100 Consecutive Cases

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ABSTRACT: The first 100 deaths caused by propoxyphene and recorded by the Chief Medical Examiner of North Carolina were studied. Victims ranged evenly in age from the second to the seventh decade. Over 65% were suicides with a female to male ratio of 2:1. Blood propoxyphene concentrations of 0.2 mg/dl were fatal, representing rapid ingestion of approximately ten capsules. In North Carolina, deaths due to propoxyphene have increased from five in 1969 to 49 in 1975. Raising physician-awareness of propoxyphene's toxicity and placing the drug in Schedule II are two of the authors' recommendations for reducing the number of propoxyphene deaths.

PROPOXYPHENE, usually sold as Darvon or some variant thereof, is a centrally acting narcotic analgesic. It has immense clinical popularity, questionable effectiveness, and poorly recognized toxicity. Propoxyphene was first marketed (as Darvon) in 1959. The first report of a death from overdose was published in 1964.[1] Subsequent articles on propoxyphene deaths and abuse were reviewed in the May 1973 report of the Bureau of Narcotics and Dangerous Drugs.[2]

The first known cases in North Carolina, the source of the present report, were certified in 1969 when five were identified. More than 170 have been documented in this state since then, most in the past five years. Although the state's Medical Examiner System and toxicology facilities began in 1968, many of the state's 100 counties and 5.3 million population have been represented only since Jan 1, 1972. We are reporting our first 100 propoxyphene deaths from that date. This is the first published study from a large state and is intended to provide insight into the problem of propoxyphene poisoning.

MATERIALS AND METHODS

Case records of the state's Office of the Chief Medical Examiner (OCME) constitute the data base for this study. All "unusual, unnatural or suspicious" deaths are reported to physician county medical examiners. They investigate the deaths and authorize further examination if indicated (eg, autopsy, toxicology, or additional interviewing). Autopsies in these cases are performed by hospital pathologists serving their communities as regional pathologists. The state's OCME is responsible for appointment of these officials, quality control, instruction, guidance, record maintenance, and many of the autopsies as well as all of the toxicologic analyses.

The medical examiners and regional pathologists report specific identifying, epidemiologic, demographic, and descriptive data plus narrative and opinions. Appropriate samples are taken for toxicologic analyses when autopsy is done; blood samples only are submitted from all other cases. The reports from case investigations, autopsy, and toxicologic findings are reviewed individually by career medical examiners/forensic pathologists at the OCME. Additional investigation or death certificate modification is made when indicated.

We sought propoxyphene-related deaths from case records of the state's OCME. We did not include 12 propoxyphene deaths recorded before Jan 1, 1972, and five victims who had significant blood concentrations (0.2-0.6 mg/dl) of propoxyphene but who also had apparently fatal natural disease (four victims of coronary thrombosis or myocardial infarction and one with bilateral pneumococcal lobar pneumonia).

The reports included varying amounts of social and psychiatric history, immediate past history, and scene description for each of the 100 cases. Eighty-nine of the 100 had autopsy; toxicologic studies were done on each. Each case was reviewed independently by at least two experienced staff members for concurrence on cause and on manner of death, eg, accident versus suicide, undetermined versus suicide.

We considered death due to propoxyphene alone "pure" if (1) the blood concentration was 0.2 mg/dl or higher, or an appropriate liver concentration existed in cases where the blood sample was exhausted from other studies or was not submitted; (2) there was not a significant concentration of other drugs or alcohol; (3) no more than minor injury or natural disease was found; and (4) appropriate history and autopsy findings were described. Our "mixed" category criteria included the above except that there was also blood ethanol concentration of over 150 mg/dl (0.15%) or other drug with at least one half the minimum fatal concentration accepted by recognized sources.[3-5]

We classified as accidental the deaths of those victims with relatively low propoxyphene levels who had high ethanol levels and whose behavior immediately preceding death was not an apparent variation from their usual. Deaths of many of the victims with a strong history of "drug abuse" were termed accidental. The suicide classification included those with previous suicide attempts, evidence of depression or disassociation, and ingestion—by a competent adult—of so many tablets or capsules in a short time so that accident seemed precluded. The manner of death was ruled undetermined when the evidence for suicide was approximately equal to that for accident.

RESULTS

Propoxyphene accounted for more deaths in North Carolina in 1975 than any other drug, excluding acute ethanol poisoning. With the 49 identified in 1975, the total rose to 136 in seven years. The detailed data are from the 100 consecutive cases from January 1972 to August 1975.

A majority of propoxyphene deaths were clearly suicides, comprising 65 of the 100 (Table). Women

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TABLE. One Hundred Consecutive Propoxyphene Deaths by Manner of Death, Sex, and Presence of Significant Levels of Other Drugs, Including Ethanol

	Suicide		*Accident*		*Undetermined*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Pure*	15	31	4	6	5	4
Mixed†	5	14	11	2	2	1
Subtotal	20	45	15	8	7	5
Total	65		23		12	

*Blood concentration of propoxyphene 0.2 mg/dl or higher, no significant concentrations of other drugs or alcohol.
†Blood concentration of propoxyphene 0.2 mg/dl or higher, plus blood ethanol concentration of over 150 mg/dl or other drug with at least one half the minimum fatal concentration.

were overrepresented, 58 to 42 overall and 45 to 20 among certified suicides. Men dominated in the accidental group, commonly having high blood alcohol concentrations at the time of death and a history of drug and alcohol abuse.

Propoxyphene deaths were relatively evenly distributed among the age groups from the last half of the second decade through the sixth, although the fifth decade did account for 30 of the 100. There was no marked age difference among the suicides, accidents, or undetermined groups or between men and women. A small number (eight) of propoxyphene victims whose deaths were judged accidental and who had no other significant detectable drugs, including alcohol, had a lower average age (26 years) than other groups. The average age for other groups was about 40 years regardless of sex, manner of death, or presence of drugs or alcohol.

Thirteen of the 100 victims were black, the remainder white. There were no marked racial differences in manner of death, age, sex, or presence of other drugs.

Blood propoxyphene concentrations were obtained in 51 of the 65 deaths that involved no significant concentration of other drugs or alcohol. The average concentration was 0.8 mg/dl, the range 0.2 mg/dl to 2.7 mg/dl. In the same 65, the 47 liver propoxyphene concentrations averaged 9.8 mg/dl and ranged from 0.8 mg/dl to 33.0 mg/dl. In 37 of the 65, propoxyphene analyses were done on both liver and blood. Twenty of the 35 "mixed" deaths had ethanol as the only other drug present having a possible significant concentration. The mean blood ethanol concentration was 200 mg/dl among the 20. Blood propoxyphene concentrations were available in 19 of the 20, the mean of these was 0.5 mg/dl; liver concentrations were available in 13 with a mean of 1.4 mg/dl. The remaining 15 of these "mixed" deaths with a fatal level of propoxyphene included as other possible significant drugs, salicylates (3), meprobamate (2), phenobarbital, secobarbital, amobarbital, butabarbital, ethchlorvynol, diazepam, amitriptyline, methadone, a possible hydrocarbon, and a combination of isopropyl alcohol, thioridazine, and secobarbital.

Usually the propoxyphene had been prescribed for the eventual victim. Prescription size, when known, ranged from 20 to 240, with 50 to 100 capsules the usual range. The specific commercial preparation of propoxyphene was known in one third of the cases. All but two of the formulations were Darvon or Darvon based, eg, Darvon Compound-65 and Darvon-N100.

Death occurred rapidly in the majority of the victims. Over 50% had been seen alive two hours or less before being found dead. Frequently, the acute collapse and death were witnessed. Approximately 30% were found dead in bed and close approximation of the time between ingestion and death was not possible. The remaining 20% include primarily those living three hours or more and those with unknown time of ingestion or death.

History of depression, previous suicide attempt, statement of suicidal intent, and suicide notes were common but not sufficient to present significant frequency data in a group of this size. Individual reports offered history of various forms of drug abuse in 26 instances, 14 of these being primarily alcohol abuse. Chronic, partially disabling physical problems such as rheumatoid arthritis, pancreatitis, and persistent back and leg injury were noted in 14 victims.

Autopsy served principally to eliminate other causes of death. The lungs were typically congested and edematous, 80% of them weighing 800 gm or more. The average weight was 1,000 gm. Abundant white froth was commonly observed in the respiratory tract. Pink-stained gastric content or other visually detectable evidence of medicinal material in the stomach was noted in approximately 10%. Fatty vacuolization of hepatic cells beyond a trace or "plus-minus" degree was present in approximately 50% of the victims.

DISCUSSION

Recognition of a large and increasing number of propoxyphene deaths in North Carolina lead us to examine several aspects of the apparent problem. These include: (1) diagnostic criteria; (2) increase in case frequency; (3) experience in other parts of the nation; (4) characteristics of population affected; (5) sources of the drug; and (6) popularity and efficacy.

(1) *Diagnostic Criteria.* The individual diagnoses were made deductively from the case histories, from autopsies that yielded no anatomic explanation for death, and from toxicologic analyses that revealed propoxyphene blood levels at least tenfold greater than the therapeutic levels. Our experience indicates a propoxyphene blood level of 0.2 mg/dl is adequate to cause death. This is consistent with the published work of others.[6,7] We believe it possible that some of our subjects with that level might have survived without the additive effect of alcohol or other drugs.

(2) *Increase in Case Frequency.* The number of deaths associated with poisoning due to drugs or other chemicals is difficult to measure in large population groups in the United States and in the nation as a whole. The paucity of adequate statewide systems for the investigation of suspicious or unnatural deaths, the unavoidable provincialism of otherwise competent county-city investigative systems, and the relative immaturity of forensic medicine in the United States give little and late data on the hazards of many drugs, poisons, and other chemicals.

We have seen an increase from rare cases from 1969 to 1971 to over a score each year from 1972 to 1974.

Forty-nine propoxyphene victims were certified in 1975. This increase may be due largely to enhanced suspicion, search efforts, and new technics. The unsupervised lay coroners who preceded the development of our Medical Examiner System had little knowledge or stimulus to obtain tests for propoxyphene or other drugs. There was no system providing a knowledgeable person to counsel the investigations or laboratory support when drugs were suspected.

At present, the county medical examiners in North Carolina are guided to consider each death investigated as possibly drug related. Furthermore, each case is reviewed at the OCME by the Chief Toxicologist and a forensic pathologist who can order additional toxicologic studies.

The technics for detection of propoxyphene have been refined during the past five years. An inadequate spectrophotometric method was improved in 1972[8] and further improved in 1974.[9] Gas chromatography is now our analytical method of preference because it allows detection of blood propoxyphene and its active metabolite norpropoxyphene.[10] The former method detects propoxyphene but only part of the norpropoxyphene. Technics that are inferior in sensitivity and specificity to both methods are still being used in many laboratories. A recent national survey[11] of toxicologic laboratories reported 50 to 138 responding toxicology laboratories did not test for propoxyphene; nine indicated a negative result on the proficiency test samples; 24 reported detection but no quantitation. Of the 54 attempting quantitation, only 16 were within 30% of the correct concentration; of these 16, only five, including ours, were within 10%.

We believe the improvements in the local medical examiner investigation and in technics for detecting propoxyphene were primarily responsible for the increase in propoxyphene deaths from four in 1971 to 22 in 1972. The jump from 28 cases in 1974 to 49 in 1975 is alarming since the system and technics did not change drastically. Our toxicologic data indicate the rise is associated with a shift in popularity of drugs. Barbiturates had been identified in more drug deaths than any other agent until 1975. In that year deaths from barbiturates decreased while propoxyphene fatalities increased and other miscellaneous and fatal drug deaths showed no significant change. We offer no adequate explanation for the marked shift.

(3) *Experience in Other Parts of the Nation.* In 1973 Sturner and Garriott[7] reported from Dallas 49 deaths involving propoxyphene among which ten were due to propoxyphene alone, 12 to propoxyphene and ethanol, and two to propoxyphene with other drugs. In 1973 the Drug Control Division of the Bureau of Narcotics and Dangerous Drugs (BNDD) reported propoxyphene data including death cases from 34 states during the years 1971 and 1972.[2] Propoxyphene was judged solely responsible for 230 deaths and contributing in 27 others in the BNDD study. Our contacts with other medical examiner systems and coroner offices indicate distinct increases. A recent national survey[12] has uncovered over 1,000 propoxyphene deaths between 1972 and 1974 in selected medical examiner systems and coroner offices. These data suggest propoxyphene deaths are not a local or regional phenomenon.

(4) *Characteristics of the Population Affected.* Propoxyphene deaths occur at all ages. In our study the fifth decade accounted for 30% of the 100 deaths with the average age of approximately 40 years for both women and men. There were few deaths among the younger adults and adolescents, a group popularly associated with "drug abuse." We did find that "pure" propoxyphene deaths which were ruled accidental did occur at a younger average age (26), although the number (eight) was small. This is consistent with the data from Sturner and Garriott[7] and with the BNDD report.[2]

There was good evidence that 65% of the propoxyphene victims committed suicide. However, many if not all of the 12 certified as undetermined and some of the less than thoroughly convincing accidents also may have been suicide. This statement reflects our conviction that rapid ingestion of enough pills (ie, 10 to 20 65-mg propoxyphene capsules) to cause death occurs as a result of a purposeful abuse by a knowledgeable person, an accidental ingestion by a curious child, or a deliberate consumption by a suicidal individual. Automatism has been a proposed mechanism in drug deaths but we and others disagree with the reasoning.[13,14] Among the deaths which the OCME and local medical examiners agreed to classify as undetermined, many victims would have had to ingest 20 or more 65 mg capsules within a short period of time. Some of those ruled accidental due to high blood alcohol concentrations involved the subject quickly consuming 10 to 15 capsules. We estimate 80% to 85% of the persons dying from propoxyphene consumption committed suicide, leaving 15% to 20% for accidental and abuse-related deaths.

Women outnumbered men more than two to one among the clearly defined propoxyphene suicides (45 of 65). By comparison, the 1974 total drug suicide cases included 56 women and 27 men. Total suicides by all agents included 189 women, 507 men. There was no significant difference between the sex ratio in propoxyphene suicides and total drug suicides. The relatively larger proportion of men in the accident and undetermined manner of death group appears to be due to their greater frequency of alcohol consumption with drug abuse. We have not found that prejudice regarding gender and drug use was a significant factor in determination of manner of death, eg, assuming an overdose death was accidental rather than a suicide primarily because the victim was male.

We were not surprised to find that at least one quarter of the cases involved persons with a history of drug abuse and that 14 of these were alcoholics. Our autopsy data indicate that approximately one half of the 100 victims may have abused alcohol; over 50% had fatty changes in the liver. This finding does not contradict the death reports, for many of them are not detailed beyond the immediate circumstances of death. The 14

histories of chronic illness and disability such as back pain might be anticipated. Both the alcohol-drug and chronic disability groups are at high risk for drug-related deaths in our experience.

(5) *Source of Drugs.* The source of the propoxyphene was the victim's own prescription in the majority of the cases. We were impressed with the frequency with which the fatal overdose closely followed a prescription refill. A relative or friend's prescription was the source for several deaths. Instances of theft or other illicit sources were rare. Sturner and Garriott[7] reported that in at least 31 of their 41 propoxyphene-involved deaths the source was the victim's prescription.

Prescription size was reported to us in less than one third of the cases. The smallest was twenty 65 mg capsules, the largest 240 (about 20 times the lethal dose). The majority were for 40 or more; 100 or greater was common. Several patients had a refill or a second propoxyphene prescription in addition to part of the original prescription. The prescription of 120 or more dose forms was most frequent at Veterans Administration Hospitals.

(6) *Popularity and Efficacy.* Propoxyphene has been number one among prescriptions dispensed in retail pharmacies in the US since the late 1960s.[15] As Darvon and Darvon-N individually, and with their various additives, propoxyphene has even surpassed diazepam (Valium) in prescription popularity. The drug has been vigorously promoted as safe through advertising and detailing. Its trade name seems pleasant and easy to remember; the capsules and compressed tablet forms are relatively attractive. Prescribing physicians and pharmacists inform us that public and private third-party compensation pays for propoxyphene but not for aspirin. Presently classified as an uncontrolled substance, propoxyphene is obviously easier to prescribe than controlled analgesics. Further enhancing its usage is the reaction of the patient who thinks that he is getting more attention if he receives attractive capsules or colored compressed tablets rather than soft, white tablets he knows are aspirin purchasable without prescription. One major review noted, "It appears that factors other than intrinsic therapeutic value are responsible for the commercial success of propoxyphene."[16]

In support of propoxyphene's usage, a manufacturer's representative wrote, "Darvon products have won a remarkable acceptance by patients and physicians since their introduction."[17] Investigators of analgesic effectiveness rebutted: "The implication that general acceptance of a therapeutic procedure by physicians in a given era constitutes obligate proof for effectiveness is not tenable. If this were true, we would still be bound to the mummy dust, unicorn's horn, leeching, purgatives, blood letting, and mustard plasters universally endorsed by our forebears. We must constantly offer challenge to all our sacred cows, so that our patients may be afforded the highest care at the most reasonable cost."[18]

Clinical reviews of the drug and evaluations of analgesics indicate inferiority to aspirin and other less toxic analgesics, and questionable advantage over placebos.[19] The 1973 BNDD report concluded, "Currently propoxyphene is being used clinically, (1) in place of codeine in the belief that it is equally effective and less toxic, and (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 indicates that this rationale for clinical use is incorrect."[2]

CONCLUSIONS AND RECOMMENDATIONS

We have documented a rapidly rising rate and number of propoxyphene deaths and anticipate over 1,000 propoxyphene deaths this year in the United States. Most will be suicides. Probably some of these victims would take their own lives were the propoxyphene not available. However, as a large proportion of suicide attempts are impulsive rather than planned, ready availability of an effective agent enhances chances of successful completion of the self-destructive act. Many factors that have little to do with any intrinsic effectiveness of the drug cause it to be readily available in large quantity to a vast number of people. Propoxyphene's meager therapeutic effectiveness adds irony to tragedy. Our studies and interviews have revealed repeatedly that many physicians regard the drug to be relatively innocuous, to be prescribed with impunity.

Our recommendations include the following: (1) education through standard medical channels concerning propoxyphene's analgesic and toxic effects; (2) physicians' voluntary reduction in average prescription size; (3) establishment of the same third-party payment standards for analgesics such as aspirin and acetaminophen as for propoxyphene; (4) enhanced patient warning of the hazards of combining alcohol and "pain killers" and other mood affecting drugs; and (5) placement of propoxyphene in Schedule II of the "Controlled Substances Act" of Public Law 91-513.

More discriminating prescription writing and reduced drug availability could diminish not only propoxyphene poisonings but also the total suicides and drug-related accidents.

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Dr. HUDSON. With that, I would also say that we can look at some factors that have influenced the changing numbers in our State. Beginning in late 1968, we began putting in a statewide system for the evaluation and examination and investigation of sudden, unexpected and suspicious deaths.

I believe that the onset of that system enhanced suspicion of specific designated deaths for investigation, but particularly a development of toxicology enabled us to begin to get these facts and to see the numbers go from a rare 1 or 2 or 3 up into the twenties. Then the system leveled off, as far as sophistication and techniques across the State but then the number of propoxyphene deaths continued to increase up to 50 in 1975.

With that as background, I would like to speak to some of the questions that you posed in your letter.

What does the volume of prescriptions written for propoxyphene show?

Propoxyphene has been at or very close to the top in total new prescription frequency for over 10 years. This is combining primarily the trade names of Darvon, Darvon-N 100, Darvon Comp, and others already discussed.

In view of prescription volume and prescription size, are doctors aware of the dangers of Darvon and other prescriptions containing propoxyphene?

No; I believe they could hardly have been less aware. I do hope that that is changing now.

I have seen some signs that perhaps it has in the past year.

Repeatedly I have seen physicians frankly shocked to learn of the frequency of propoxyphene fatalities.

Some stated they had heard of propoxyphene victims but assumed they were "young punks shooting drugs" as opposed to the kinds of folks their own patients represented.

The reactions have varied from, "I think it is a good drug, my patients ask for it." to "I don't know why I use it; it isn't worth a damn without aspirin in it."

Is it sound practice to prescribe 120 or more dose forms of propoxyphene, as you have found done most frequently at Veterans' Administration hospitals?

In my opinion, no.

I realize that there are severe logistical and other problems in managing chronically ill patients who live many miles from the medical centers and/or have physical or other disabilities that handicap frequent visits.

However, propoxyphene is one of the pacifiers given these patients.

Chronic use requires increasing doses for such analgesic effect as propoxyphene does have, but it has not been demonstrated that the patients develop any protection against overdose.

Twenty dose units of propoxyphene is an ample amount for 5 to 7 days of pain relief. The pain that persists longer than that signifies a need for more than a mild and hazardous analgesic.

I am familiar with Veterans' Administration hospitals, or at least several of them, and I know that a large proportion of the medication is given out to patients or outpatients to take home is intended at least to be pacifiers or placebos to some extent the patient, and perhaps

even to some extent the physician. He—the physician—wants to do something for the patient but it is particularly dangerous to give large quantities of mood-affecting drugs to patients with psychiatric, alcohol, or drug-addiction problems. But it is done commonly.

In my experience this group of hospitals has been one that stood out in my mind.

What is the medical justification for having propoxyphene on the market?

As I see it, the only justification is habit, custom, acceptance by physicians and patients.

As has been discussed, propoxyphene offers no efficacy, no more than over-the-counter preparations, but except that the over-the-counter preparations lack the "psychic" authority of prescription drugs.

Also, there is more magic in having a prescription than something which somebody obtained over-the-counter which seemingly would not be that effective or give that same effect.

It—nonprescription medication such as aspirin—is not that impressive to the patient.

I believe it is generally true the third party payees usually do not pay for aspirin, acetaminophen and the like, but they do for the prettier, more expensive, less effective propoxyphene.

Do the benefits of the drug outweigh its risks?

No. The benefits are minimal if indeed they exist. The risks are the demonstrated frequency of drug abuse, accidental combination with other central nervous system depressants, and availability to the potential suicide victim, among others.

In your experience, what is the relative abuse liability of propoxyphene and codeine?

I do not know what the abuse frequency and addiction severity would be if the two drugs were used by equal numbers and types of people at equivalent dose levels. I believe no one knows.

There is inexplicably an awareness within the medical profession of addiction potential of codeine but the proper awareness has not yet developed for propoxyphene.

The margin of safety for codeine may be greater than that of propoxyphene.

There have been hundreds of proven deaths from propoxyphene for every one documented for codeine. I see no logic in having codiene in schedule II with propoxyphene in schedule IV.

We are aware of some 200 or so of propoxyphene deaths in North Carolina during the same period of time; we have been able to identify three deaths that primarily used codeine.

Your last question, please discuss the nature and extent of DAWN deaths involving propoxyphene, including the manner of classification of these deaths as suicidal, accidental, or undetermined, and the role of toxicologic analyses of blood, liver, and tissue in determining the presence of propoxyphene and its chief metabolite.

If I may, I for one have not been impressed with the DAWN data, primarily because of its vagueness, more specifically to the term "drug related."

The definitive identification, or what to me approaches the definitive identification of a drug is not only the history of the opportunity

to abuse that drug in statements by friends of the victims, but reasonable efforts to rule out other causes of death, and best yet, toxological determination, that particular form of chemistry that detects the drug and measures it and demonstrates it to be in sufficient quantity to cause death.

Most of the cases referred to in the DAWN material seems to me from my readings not to reflect that quality of data, that quality of verification of drug-related data necessary as far as specific drugs are concerned.

In our own State, as far as manner of death is concerned, we believe that with rather careful review that approximately two-thirds or three-quarters of the deaths are suicide. I am chagrined that our American social and medical systems in a broad sense, have allowed this to come about, that this drug which has been available for 20 years, has been accounting for as many or more drug deaths than any other for so many years, and we have such a lack of awareness generally within and without the medical profession.

Thank you.

Senator NELSON. Thank you very much, Doctor.

Dr. HUDSON. Thank you.

[The prepared statement of Dr. Hudson follows:]

STATEMENT OF PAGE HUDSON, M.D., CHIEF MEDICAL EXAMINER (NORTH CAROLINA); PROFESSOR AND CHAIRMAN OF DIVISION OF FORENSIC PATHOLOGY, UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE, CHAPEL HILL, N.C.

I am a doctor of medicine specializing in forensic pathology and am certified by the American Board of Pathology in anatomic pathology and in forensic pathology. Forensic pathology is that medical specialty that involves the detection, identification, investigation and other studies of real or suspected unnatural deaths. I practice, write and teach in this field of medicine and related sciences. My employment is as Chief Medical Examiner. My appearance here is with the permission of North Carolina's Division of Health Services, Department of Human Resources; however I choose to volunteer that my opinions are my own as a private citizen and do not represent an official stance or policy of North Carolina.

It became apparent several years ago that propoxyphene was responsible for increasing numbers of deaths in North Carolina. Dr. Arthur J. McBay who is Chief Toxicologist to the Office of the Chief Medical Examiner and I examined our cases, methods, criteria and diagnoses. We conferred with authorities in other states and with many physicians involved daily with patient care. We got the strange feeling that we were among the first discoverers of a relatively obvious and moderately awesome phenomenon: A drug medication existed that was at the top in prescription popularity, one that had but a trace of benefit and that was reaching the point of causing more deaths than any drug, licit or illicit, in this country.

We published data and our concerns in a letter in the Journal of the American Medical Association in September 1975. After further developing our data we published an article about propoxyphene hazards in the Southern Medical Journal in August 1977. Copies of this have been made available to you with copies of my statement. The article still expresses my sentiments, those of Dr. McBay I believe and those of Dr. Michael Barringer, a surgeon who was a medical student when he co-authored the article. Dr. McBay and colleagues have published on their improved techniques for detecting and measuring propoxyphene.

Our concept of the more cogent elements of our article is as follows: Our data are from a statewide death investigation system covering a state of about 5.5 million people. We believe inferences can legitimately be drawn from our data that can be extended to the national population. The number of deaths associated with poisoning due to drugs or other chemicals is difficult to measure in large population groups in the United States and in the nation as a whole.

The paucity of adequate statewide systems for the investigation of suspicious or unnatural deaths, the unavoidable provincialism of otherwise competent county-city investigative systems, and the relative immaturity for forensic medicine in the United States give little and late data on the hazards of many drugs, poisons and other chemicals.

We have seen an increase in propoxyphene deaths from rare cases in 1969 through 1971 to over a score annually from 1972 through 1974. Forty-nine were certified in 1975. Subsequent years have yielded at least 30 each. Development of the new medical examiner system with enhanced suspicions, search efforts, and new toxicology techniques may have accounted for the initial increase. There was another surge in propoxyphene deaths well after our medical examiner system was stabilized.

Reports from other investigators including the BNDD (now DEA) indicate the North Carolina experience is not a regional phenomenon.. At least 65, perhaps 80 percent of the deaths are suicides. The drug the victims used had been prescribed for them in most instances. Ten dose units appeared adequate to cause death but more were generally used. The prescription size ranged from 20 to 240 units. Females were predominant except among the "accidental overdoses". Alcohol and other drugs were commonly present, *usually not* in significant quantity (and not really more frequently or at greater concentrations than detected with gunshot suicides).

The great popularity of propoxyphene (almost entirely Darvon, Darvon Comp 65, Darvon-N 100 and the like) appears to be due to factors other than its effectiveness. These appear to include:

(a) Vigorous marketing and detailing efforts.
(b) Fortunate name.
(c) Attractive appearance.
(d) Third party compensation for propoxyphene but not for aspirin or acetaminophen.
(e) Public concept of the drug as a "real" medicine as opposed to plain aspirin.
(f) Physicians' concept of the drug as essentially harmless.

Independent evaluations of analgesics generally rank propoxyphene as equivalent to placebo and less efficient than aspirin.

Our recommendations included:

(1) Education through standard medical channels concerning propoxyphene's analgesic effects.
(2) Physicians' voluntary reduction in average prescription size.
(3) Establishment of the same third party payment standards for analgesics such as aspirin and acetaminophen as for propoxyhene.
(4) Enhanced patient warning of the hazards of combining alcohol and "pain killers" and other mood affecting drugs.
(5) Placement of propoxyphene in Schedule II of the "Controlled Substances Act" of Public Law 91–513.

We concluded with the opinion that "more discriminating prescription writing and reduced drug availability could diminish not only propoxyphene poisonings but also the total suicides and drug-related deaths".

Some of the other issues discussed in the article are addressed in my responses to the following questions posed in Senator Nelson's invitation to appear here today.

Q. What does the volume of prescriptions written for propoxyphene show?

A. Propoxyphene has been at or very close to the top in total new prescription frequency for over 10 years. This is combining primarily the trade names of Darvon, Darvon N 100, Darvon Comp and others.

Q. In view of prescription volume and prescription size, are doctors aware of the dangers of Darvon and other prescriptions containing propoxyphene?

A. No. They could hardly have been less aware. Repeatedly I have seen physicians frankly shocked to learn of the frequency of propoxyphene fatalities. Some stated they had heard of propoxyphene victims but assumed they were "young punks shooting drugs" as opposed to the kinds of folks their own patients represented. Reactions have varied from, "I think it's a good drug, my patients ask for it", to, "I don't know why I use it; it isn't worth a damn without aspirin in it."

Q. Is it sound practice to prescribe 120 or more dose forms of propoxyphene, as you have found done most frequently at Veterans Administration hospitals?

A. No. I realize that there are severe logistical and other problems in managing chronically ill patients who live many miles from the medical centers and/

or who have physical or other disabilities that handicap frequent visits. However, propoxyphene does is one of the pacifiers given these patients, diazepam (Valium) another. Chronic use requires increasing doses for such analgesic effect as propoxyphene does have but it has not been demonstrated that the patients develop any protection against overdose. Twenty dose units of propoxyphene is an ample amount for 5–7 days of pain relief. The pain that persists longer than that signifies a need for more than a mild (and hazardous) analgesic. I have worked with VA hospitals and know that a large proportion of the medication given outpatients or patients to take home are intended, at least in part, to be placebos or pacifiers to aid the patient in believing he is being helped and to keep him from bellyaching such as by writing his representative or senator. It is particularly dangerous to give large quantities of mood-affecting drugs to patients with psychiatric, alcohol or drug-addiction problems. But it is done commonly. The VA hospitals stand out in my mind in this regard.

Q. What is the medical justification for having propoxyphene on the market?

A. The only justification is habit, custom, acceptance by physicians and patients. There are cheaper, safer, more effective mild analgesics than propoxyphene readily available, even over-the-counter (OTC) preparations. But OTC's lack the psychic authority of prescription drugs. Also, third party payees usually do not pay for aspirin, acetaminophen and the like but they do for the prettier, more expensive, less effective propoxyphene.

Q. Do the benefits of the drug outweigh its risks?

A. No. The benefits are minimal if indeed they exist; the risks are the demonstrated frequency of drug abuse, accidental combination with other central nervous system depressants, and availability to the potential suicide victim, among others.

Q. In your experience, what is the relative abuse liability of propoxyphene and codeine?

A. I do not know what the abuse frequency and addiction severity would be if the two drugs were used by equal numbers and types of people at equivalent dose levels. I believe no one knows. There is inexplicably an awareness within the medical profession of addiction potential of codeine but the proper awareness has not yet developed for propoxyphene. The margin of safety for codeine may be greater than that of propoxyphene. There have been hundreds of proven deaths from propoxyphene for every one documented for codeine. I see no logic in having codeine in Schedule II with propoxyphene in Schedule IV.

Q. Also please discuss the nature and extent of DAWN deaths involving propoxyphene including the manner of classification of these deaths as suicidal, accidental or undetermined, and the role of toxicologic analyses of blood, liver and tissue in determining the presence of propoxyphene and its chief metabolite.

A. The North Carolina propoxyphene manner of death data are referred to in the Hudson, Barringer, McBay reprint, last paragraph of its front sheet, page 938; also the succeeding paragraph on the following page; particularly the three paragraphs on page 940 of the article.

Relative to manner of death, I disagree with the recent published statement by the very able medical examiner/forensic pathologist from the excellent medical examiner system in Oregon. He, I believe, contends that the majority of the propoxyphene deaths are accidents due to the buildup in the body of propoxyphene's chief break-down product or metabolite, norpropoxyphene. The explanation of our difference is somewhat long and technical and I shall not go into that now unless requested to. It does concern the understanding of propoxyphene metabolism and interpretation of toxicological testing results. I believe most toxicologists and forensic pathologists who have studied the matter agree with Dr. McBay and me that the majority of the deaths are suicide. An exception is an able group in a county in California. There I believe it is the custom to certify many drug overdoses as accident in the absence of a suicide threat or note in spite of chemical and other evidence that the deceased took 20–30 capsules a short time before death.

The concentration of propoxyphene in blood, as revealed by appropriate toxicological analysis is the best indication of the number of dose units ingested. The norpropoxyphene disappears much more slowly from the blood than propoxyphene. Its presence reflects the size of the recent dose and the survival time following that dose, but also may represent buildup or accumulation from normal doses—or a combination of the two, e.g., normal dosage for a few days plus a very recent,

massive, fatal dose of propoxyphene. We now consider liver concentrations to rarely be of value.

In conclusion, I as a physician am chagrined with the role that the medical "sciences" have had in the availability of the drug propoxyphene. If my concept of the current scope and function of the Food and Drug Administration (FDA) is correct, I do not believe it would license propoxyphene if that drug were being offered now as a new medication, on the grounds of inadequate efficiency alone.

PAGE HUDSON, M.D.

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Senator NELSON. I will now call on Dr. Arthur J. McBay, chief toxicologist, office of the chief medical examiner, Chapel Hill, N.C.

STATEMENT OF ARTHUR J. McBAY, CHIEF TOXICOLOGIST, OFFICE OF THE CHIEF MEDICAL EXAMINER, CHAPEL HILL, N.C.

Dr. McBAY. Senator Nelson, Senator Morgan, and members of the committee.

I do not know whether you want me to recite part of my background or what.

I have not got it in my statement.

Senator NELSON. It is not in your statement?

Dr. McBAY. No.

Senator NELSON. For the record it would be helpful to recite it.

Dr. McBAY. Fine.

I have a bachelor degree and a master of science degree in pharmacy. I have been a registered pharmacist since 1940, although I am not actively practicing pharmacy.

I have a Ph. D. degree from Purdue University, 1948, in medicinal chemistry. I was a member of the department of legal medicine at Harvard Medical School for about 10 years, and my principal job at that time was supervisor of the Massachusetts Department of Public Safety Laboratory.

This is a crime laboratory. My principal efforts were in either homicide or toxicology investigations.

In 1969, I became chief toxicologist for the State of North Carolina, and for the office of the chief medical examiner, and I was made a member of the staff of the department of pathology and department of pharmacy of the University of North Carolina.

At the time, I am a full professor in both departments. I am board certified in toxicology and forensic toxicology.

I am a member of several toxicological societies, pharmaceutical society, National Safety Council on Alcoholic and Drugs.

Senator MORGAN. Were you on the North Carolina Drug Authority?

Dr. MCBAY. Yes, I was. We were together.

Senator MORGAN. I thought you were.

Dr. MCBAY. Propoxyphene had been the most frequently prescribed analgesic until 1976, when Tylenol with codeine (CIII), and until 1977, when Empirin Compound with codeine (CIII), exceeded it in popularity.

It was the second most frequent prescription in 1971 and 1972.

It has been reported that 33.5-million prescriptions were dispensed in 1977 containing propoxyphene.

In our opinion, the acute adult oral lethal dose is about 12–20, 65-mg. doses, or over 800 mg. In those deaths where the number of prescribed doses were reported, the smallest was for 20, 65-mg. capsules, the largest 240—more than 20 times the lethal dose.

The majority were for 40 or more; 100 or greater was common.

Several patients had a refill or a second propoxyphene prescription. The prescription of 120 or more doses was most frequent at Veterans' Administration Hospitals. There is obviously great danger in allowing a patient to have access to large amounts of this drug.

Although we are mainly concerned with deaths resulting from overdoses of this drug, something should be said about the value of this drug as an analgesic.

If it were a unique and valuable analgesic which was useful where other analgesics could not or would not be efficient, then the benefits of this drug might outweigh the costs.

Of the many reports on this substance as an analgesic, there are practically no adequately controlled studies which demonstrate a significantly greater analgesic effect than other analgesics such as aspirin, actaminophen, and codeine; some studies report the drug as not significantly more efficient than a placebo.

I am principally concerned with the toxicity of this drug and the ultimate toxicity that kills people.

I would like to state when there is an overdose, and certainly if anybody takes the recommended dose of most drugs, they should not die as a result of taking them.

I am sure that people have taken as much as 1,800 mg. or as much as 2,000 mg. of this drug and survived, going into withdrawal if the drug is discontinued abruptly.

But I have very little faith in the reported data, but whenever it was reported, and whenever we could track it down, the smallest dose was for about 20, 65-mg. capsules, the largest was for 240, which is more than 20 times the lethal dose.

The majority with 40 or more, and 100 or greater, was common.

In some of the data in the drug abuse warning prescription audits, somewhere around 35 to 40 doses seemed to be the average prescription size.

I am not qualifying myself on the efficiency of this drug, but I do have to teach students about this drug, and I can give the relative toxicity without discussing benefits.

If it is a very beneficial drug, the chance must be taken the individual will not take an overdose.

In the past 5 years in North Carolina, 183 deaths were attributed to propoxyphene, 26 were attributed to salicylates (aspirin), 3 to codeine, and none to acetaminophen.

We believe these data are similar to those from the relatively few communities having adequate death investigation systems including toxicology.

In our opinion, overdoses from these other drugs which are used more frequently than propoxyphene are much safer at least as far as fatalities are concerned.

The most serious problem with dextropropoxyphene is that overdoses often lead to death. With the advent of better analytical methods, it soon became apparent that deaths were being attributed to this drug.

Obviously we do not try to detect it when nobody suspects the drug is causing deaths, so those deaths will not be attributed to the drug.

In our laboratory the following numbers of cases were documented:

1970	3
1971	2
1972	21
1973	21
1974	30
1975	50
1976	34
1977	36
1978	31

Our data is complete for 1978, unless we discover some mistake, it is 31, so there is no question that the deaths are there.

In the last 5 years 183 deaths have been reported in North Carolina which has a population of about 5.5 million.

It is the 11th most populous State.

If the death rate for the entire United States was the same there would be at least 1,200 deaths yearly of discovered deaths for the country in 1978.

The reported deaths are those that are discovered. There is no way of ascertaining how many deaths are due to the drug that are not attributed to the drug.

Propoxyphene is ranked as third in frequency of occurrence in deaths reported in DAWN VI, which is the Drug Abuse Warning Network publication.

It is preceded by alcohol in combination and heroin/morphine. In North Carolina and in seven standard metropolitan areas it is a more frequent cause of death than heroin, as it probably is in most of this country.

The majority of deaths are suicidal in North Carolina when the manner of death could be determined. Many of the deaths attributed to

overdoses of propoxyphene involve other drugs including alcohol and diazepam.

In the deaths we have attributed to propoxyphene there was in our opinion, and I am sure Dr. Hudson has read this and agrees with me, there was a sufficient quantity of the drug to cause death in the absence of the other drugs but the other drugs may have been contributory factors in the deaths.

Of the 183 deaths attributed to propoxyphene at least 145 or about 80 percent did not have enough alcohol or any other drug that we found to have caused death; in each sufficient propoxyphene to cause death was found, at least in our opinion.

In seven cases greater than 20 mg/dl of salicylate was found. This could come from a propoxyphene-aspirin containing product.

Of course, we have no way of knowing if somebody takes propoxyphene alone, or aspirin alone, or they take another product with it.

Most of our cases involved deaths of middle-aged individuals and not the younger drug abusers.

In fact, I do not recall any deaths in the young abusers, certainly not by injecting the drug.

Although propoxyphene was introduced in 1957, it was not until around 1970 that analytical procedures for adequately detecting and measuring it in the relatively low concentrations present in the blood of those fatally poisoned began to be reported.

Twelve articles of propoxyphene overdoses published from 1960–70 reported four fatalities. This is in the literature.

Eighteen articles published from 1971–75 reported 117 fatalities.

A survey published in 1976, reported 1,022 propoxyphene-associated cases in the years 1969 through July 1975.

There were only 2 in 1969, 7 in 1970, and 11 in 1971 for a total of 20 cases.

And, 1,002 cases were reported for the 3½ years 1972–July 1975.

This survey covered a 5-year period and covered approximately one-fifth of the United States. It was the same areas each year. In the same 9 years, 1970–78 we have discovered 228 fatal overdoses in North Carolina.

In spite of greatly improved analytical procedures which allow for the identification and quantification of not only the parent drug propoxyphene, but also its longer-lived pharmacologically active metabolite, nor-propoxyphene, many laboratories either do not detect the drug or are unable to quantitate it and its metabolite.

In establishing that the drug is a cause of death it is essential that about one microgram of propoxyphene be found in a milliter of blood and not be confused with the usually greater concentration of nor-propoxyphene, the metabolite.

A therapeutic dose of 130 milligrams (two 65-mg doses) of propoxyphene hydrochloride produces concentrations of the order of 0.1 mcg/ml of blood. This is about one-tenth what we consider a lethal blood concentration.

In a national proficiency testing program in 1978, and others are similar, which involved 273 laboratories, 120 laboratories reported that propoxyphene was identified and nor-propoxyphene was identified by 32.

Only 67 reported quantitative results for propoxyphene with a range of 0.7–13.0 mcg/ml for a serum containing 5 mcg/ml and 13 reported a range of 0.3–3.0 mcg/ml of nor-propoxyphene for a serum containing 2 mcg/ml.

The specimen which contained about five times the lethal concentration was identified by about only 44 percent of the laboratories and quantitated by about 25 percent with a very wide range of results.

This could serve as an evaluation of the state-of-the-art of analysis for the drug in 1978.

We infer that many cases are missed because of generalized inadequacy of the laboratories.

In 1971 when the patent on propoxyphene hydrochloride expired, propoxyphene napsylate was introduced. It was hoped that its lower solubility would prevent poisoning by overdoses, unfortunately we have seen no evidence of this.

In 1978 in North Carolina where 31 deaths were attributed to propoxyphene, the trade names were given in the histories on 17 reports.

Thirteen had the trade names of one manufacturer; eight were for a propoxyphene hydrochloride product and six were for a propoxyphene napsylate product; one case had both names.

Hopefully propoxyphene napsylate would not be absorbed as rapidly and could prevent a large overdose from hitting the patient at one time.

Unfortunately, we have seen no evidence of this, and it is hearsay, but it is all we have to go on when the patient is dead.

We cannot talk to him.

Here we are talking of not only a sole manufacturer or distributor for propoxyphene. There are quite a number, 17 or more, I do not know how many there are.

Our attention was attracted to the drug in 1972 when we applied a specific method of analysis developed in our laboratory to specimens submitted from a number of unexplained deaths.

We were not the only ones to have specific methods of analysis at that time.

If an adequate method of analysis for the drug had existed, it is interesting to speculate whether overdose deaths would have been detected and if they had, would the use of the drug have been discouraged.

If propoxyphene were not legally available, it is our opinion that there would be no incentive to prepare the compound or to traffic in this drug for the illicit market.

We have been asked to comment on DAWN death data. I have been critical in the past, and I continue to be critical of the data as far as deaths are concerned, and I can comment only on the material made available to us.

We do not buy the service. Occasionally I see the material printed in the literature, and occasionally some has been supplied to me.

My criticism centers around what appears to be a great deal of the data that is generated on "mentions" of drugs.

In our experience drugs mentioned by emergency room personnel or by medical examiners which we assume have been mentioned by the patient or others may be entirely different from those found by toxicological analysis.

We value this information, but we are not a bit surprised to find some other drug present when the person has died, or indeed when they are in the hospital. We do some work on samples obtained from living patients.

As for the medical examiner DAWN data, it is our opinion that it is hopelessly confused in the "drug induced" or "drug related" deaths by naming drugs which may be present but may not be enough to cause death or to be a contributory cause.

This is further complicated by allowing a cause of death determination to be supported by factors other than "Toxicological Laboratory Report" (p. 8, DAWN VI).

This goes all the way down to what somebody has said about the drug.

The data would be meaningful if it was based on the cause of death as certified by the medical examiner where the determination was based on the finding of a toxicologically significant concentration of substance in the body of the deceased.

There indeed, at least the cause of death is a public record and is readily available, even without the Public Information Act, it always has been available to my knowledge.

Table 4.7, page 57 of DAWN VI indicates that there were 308 diazepam-induced deaths and 209 codeine-induced deaths.

A national survey reported that two deaths of the 1,239 "diazepam-related deaths" surveyed "could be substantiated as deaths resulting from the actions of diazepam and diazepam alone."

There were only two of these that could be substantiated.

Thus of 1,239 diazepam-related deaths, only two could be substantiated to diazepam alone.

One of these was in Canada, the other was in the United States. In North Carolina in the past 5 years we have two deaths certified as diazepam deaths and three deaths certified as codeine deaths.

We are talking about in our State of a very small number of deaths. Yet a rather large number in the DAWN data is graphically illustrated in an article where codeine was blamed for "16.6 drug-related deaths per million pills," and as a pharmacist, the last pill I have seen was a digitalis pill, so I use pills in quotes.

Propoxyphene was blamed for 1,090 deaths or "1.6 drug-related deaths per million pills."

We believe that there were far fewer than 420 codeine deaths, which is the figure given.

Using data generated by the same company there were two codeine-containing generic preparations which totaled 1,431,000 prescriptions.

Tylenol with codeine was ranked 7th in prescription frequency and Empirin compound with codeine was ranked 14th with Dalmane being ranked 13th.

What I am trying to get at, I had to use some published tables, I did not have all of the data.

The DAWN data projects 12,795,000 Dalmane prescriptions. Estimating at least 13 million prescriptions for Tylenol with codeine and 10 million for Empirin compound with codeine for a total of about 23 million codeine-containing prescriptions being used in the United States for a year, using an estimate of 36 pills per prescription could give a total of 828 million pills or 0.5 deaths per million pills.

Our projections would mean that rather than "16.6 codeine-related deaths per million pills" there would be about 1/30th that number or 0.5.

It is our opinion that more than 23 million codeine prescriptions are dispensed and that less than 100 deaths are attributable to codeine. The company that produced the statistics should be able to confirm or correct our estimates.

It appears that the deaths related to codeine were attributed to codeine "pills."

Most prescriptions for codeine are for tablets of codeine combined with aspirin or acetaminophen which were not included but represent about 98 percent of the codeine dispensed.

Had this been done in the case of propoxyphene the 1.6 propoxyphene related deaths per million "pills" would have been about 16.

In summary, the DAWN data and interpretations of it make it appear that there are many codeine deaths and that the death rate per million doses is very high and that codeine is about 10 times more lethal than propoxyphene.

We find in North Carolina that there are about 75 propoxyphene deaths to 1 codeine death.

At least from the major side effect of a drug, it is far less toxic and it is prescribed in great quantities much greater than indeed propoxyphene is.

From the survey it has also been estimated that there are about 880 Valium-related deaths. In our opinion deaths due to Valium are very rare and in our opinion should be 10 or less.

In the 1-year interval May 1976 to April 1977, 10 marihuana-related deaths have been estimated. We know of no documented death due to marihuana in the United States at anytime.

What I am saying is that projected data gives some rather strange results, and since my colleagues know of no marihuana direct death in the United States at any time, I believe they will support me, yet there is a survey that says with marihuana, there were 10 deaths by projection.

Opinions: There are at least 1,200 deaths a year in the United States due to propoxyphene.

These are estimated from reported deaths, and in my opinion this is a rather low figure.

The majority of these are suicidal overdoses from about 12 or more tablets or capsules obtained by a legal prescription. The average prescription is for about 30 dose units.

Propoxyphene was present in the majority of our cases in sufficient concentrations to cause death even if the other drugs found were not present.

Deaths would have been attributed to the drug earlier and even probably to a greater extent now, even now more frequently if adequate toxicological analyses were available.

Determination that death is caused by a drug should only be made when sufficient concentration of the drug is found in appropriate specimens and no other adequate explanation for death is found.

Propoxyphene is a narcotic, opiate, central nervous system depressant, analgesic of questionable value.

Aspirin, acetaminophen, or codeine are much safer and appear to be sufficiently effective.

Thank you, sir.

Senator NELSON. Thank you very much, Dr. McBay, for your statement.

Given your scientific judgment of marihuana. I trust that when you get back to Chapel Hill you will be very popular with the students.

Anyone have any questions?

Mr. STURGES. Mr. Chairman, just for the record, may we note that Dr. Hudson and Dr. McBay wrote to the Drug Enforcement Administration November 30, 1976, to state that, in their opinion, placing propoxyphene on schedule IV was inadequate, and recommending that the drug be placed on schedule II or, at least, schedule III. If possible, can we include this letter of theirs in the record?

Senator NELSON. Is that still your position today?

Dr. MCBAY. Yes.

Dr. HUDSON. Yes.

[The letter follows:]

OFFICE OF THE CHIEF MEDICAL EXAMINER,
Chapel Hill, N.C., November 30, 1976.

ADMINISTRATOR,
Drug Enforcement Administration, Department of Justice,
Washington, D.C.

Attention: DEA Federal Register Representative.

GENTLEMEN: We object to and protest the placing of dextropropoxyphene in Schedule IV of the Controlled Substances Act.

Our studies and others indicate that dextropropoxyphene is directly responsible for more deaths in the United States than any other prescription item, even the barbiturates collectively. (1–4, 10) It probably takes more lives than any single chemical except alcohol. Our conservative estimate is 1000 propoxyphene deaths; 2000 annually may be much closer to the truth. This is exceptionally ironic since its efficiency as an analgesic has been reported as less than that of aspirin. (5, 11) We grant that most of these deaths are suicides but suggest that in the susceptible the likelihood of attempt increases with availability of means. Classical drug abuse with propoxyphene has long been described in the medical literature. We note also the close similarity in chemical structure that dextropropoxyphene bears to methadone, a habituating narcotic.

Absurdity is heaped upon absurdity with Schedule IV placement of propoxyphene when codeine is in Schedule II. There may be abuse potential for codeine but the evidence is scant. In our combined experience with living patients and with death cases and as consultants to law enforcement agencies, we recall encountering no codeine abusers and no codeine deaths. This was true also before "scheduling" of drugs.

In our opinion abuse of dextropropoxyphene may lead to greater physical and psychological dependence than does codeine. (6–8) It is difficult for us to believe that dextropropoxyphene has a lower potential for abuse than does phenobarbital in Schedule III. We could cite other incongruities.

We have been in direct communication with officials of Eli Lilly & Company, principal marketers of dextropropoxyphene. Their public comments relative to dextropropoxyphene deaths being primarily alcohol and mixed drug problems and to being a "regional phenomenon" are to us specious and self-serving.

Admittedly there has been only relatively recently development of good chemical methods to detect dextropropoxyphene poisoning. This, added to the general lack of adequate death investigation systems in this country has contributed to a late recognition of deaths due to America's most popular analgesic prescription drug. We wonder if reticence to admit a mistake contributes to scheduling the drug no higher than Schedule IV. (9) We also speculate that if this drug had just been created, it would not be licensed by the F.D.A. because of its lack of effectiveness.

Individually and collectively we sincerely believe, on the basis of our professional experience, that dextropropoxyphene should at least be placed in Schedule III to minimize its use and abuse, but preferably placed in Schedule II with the hope that its use would be greatly discouraged.

Yours truly,

PAGE HUDSON, M.D.,
Chief Medical Examiner.
ARTHUR J. MCBAY, Ph. D.,
Chief Toxicologist.

Senator NELSON. We thank you very much for your testimony, Dr. McBay.

Dr. MCBAY. Thank you.

[The prepared statement of Dr. McBay follows:]

STATEMENT BY ARTHUR J. MCBAY, PH. D., CHIEF TOXICOLOGIST, OFFICE OF THE CHIEF MEDICAL EXAMINER, PROFESSOR OF PATHOLOGY AND PHARMACY, UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N.C.

My appearance here is with the permission of the North Carolina Division of Health Services and the Chief Medical Examiner; however the opinions I volunteer are my own as a private citizen and do not represent an official stance or policy of the state of North Carolina.

Propoxyphene had been the most frequently prescribed analgesic until 1976 when Tylenol with codeine (CIII), and until 1977 when Empirin Compound with Codeine (CIII), exceeded it in popularity (*1*). It was the second most frequent prescription in 1971 and 1972. It has been reported that 33.5 million prescriptions were dispensed in 1977 containing propoxyphene.

In our opinion the acute adult oral lethal dose is about 12–20 65-mg doses or over 800 mg. In those deaths where the number of prescribed doses were reported, the smallest was for 20, 65-mg capsules, the largest 240 (more than 20 times the lethal dose). The majority were for 40 or more; 100 or greater was common. Several patients had a refill or a second propoxyphene prescription. The prescription of 120 or more doses was most frequent at Veteran Administration Hospital (*2*). There is obviously great danger in allowing a patient to have access to large amounts of this drug.

Although we are mainly concerned with deaths resulting from overdoses of this drug, something should be said about the value of this drug as an analgesic. If it were a unique and valuable analgesic which was useful where other analgesics could not or would not be efficient, then the benefits of this drug might outweigh the costs. Of the many reports of this substance as an analgesic, there are practically no adequately controlled studies which demonstrate a significantly greater analgesic effect than other analgesics such as aspirin, actaminophen and codeine; some studies report the drug as not significantly more efficient than a placebo.

In the past 5 years in North Carolina 183 deaths were attributed to propoxyphene, 26 were attributed to salicylates (aspirin), 3 to codeine and none to acetaminophen. We believe these data are similar to those from the relatively few communities having adequate death investigation systems including toxicology. In our opinion overdoses from these other drugs which are used more frequently than propoxyphene are much safer at least as far as fatalities are concerned.

The most serious problem with dextropropoxyphene is that overdoses often lead to death. With the advent of better analytical methods it soon became apparent that deaths were being attributed to this drug. In our laboratory the following numbers of cases were documented: 1970–3, 1971–2, 1972–21, 1973–21, 1974–30, 1975–50, 1976–34, 1977–36, 1978–31. In the last 5 years 183 deaths have been reported in North Carolina which as a population of about 5.5 million. If the death rate for the entire United States was the same there would be at least 1200 deaths yearly. The reported deaths are those that are discovered. There is no way ascertaining how many deaths are due to the drug that are not attributed to the drug.

Propoxyphene is ranked as third in frequency of occurrence in deaths reported in DAWN VI. It is preceded by alcohol in combination and heorin/morphine. In North Carolina and in 7 standard metropolitan areas it is a more frequent cause of death than "heroin", as it probably is in most of this country.

The majority of deaths are suicidal in North Carolina when the manner of death could be determined (2). Many of the deaths attributed to overdoses of propoxyphene involve other drugs including alcohol and diazepam. In the deaths we have attributed to propoxyphene there was in our opinion a sufficient quantity of the drug to cause death in the absence of the other drugs but the other drugs may have been contributory factors in the deaths. Of the 183 deaths attributed to propoxyphene at least 145 or about 80% did not have enough alcohol or other drug to have caused death; in each sufficient propoxyphene to cause death was found. In 7 cases greater than 20 mg/dl of salicylate was found. This could come from a propoxyphene-aspirin containing product. Most of our cases involved deaths of middle-aged individuals and not the younger drug abusers.

Although propoxyphene was introduced in 1957, it wasn't until around 1970 that analytical procedures for adequately detecting and measuring it in the relatively low concentrations present in the blood of those fatally poisoned began to be reported. Twelve articles (3) on propoxyphene overdoses published from 1960–1970 reported 4 fatalities. Eighteen articles (3) published from 1971–1975 reported 117 fatalities. A survey published in 1976 (4), reported 1022 propoxyphene-associated cases in the years 1969 through July 1975. There were only 2 in 1969, 7 in 1970, and 11 in 1971 for a total of 20 cases; 1002 cases were reported for the 3½ years 1972–July 1975. In the same nine years, 1970–1978 we have discovered 228 fatal overdoses in North Carolina. In spite of greatly improved analytical procedures which allow for the identification and quantitation of not only the parent drug propoxyphene but also its longer-lived pharmacologically-active metabolite, norpropoxyphene, many laboratories either do not detect the drug or are unable to quantitate it and its metabolite. In establishing that the drug is a cause of death it is essential that about 1 microgram of propoxyphene be found in a milliliter of blood and not be confused with the usually greater concentration of norporpoxyphene. A therapeutic dose of 130 mg (2 65-mg doses) of propoxyphene hydrochloride produces concentrations of the order of 0.1 mcg/ml of blood. This is about one-tenth what we consider a lethal blood concentration.

In a national proficiency testing program in 1978 which involved 273 laboratories, 120 laboratories reported that propoxyphene was identified and norpropoxyphene was identified by 32. Only 67 reported quantitative results for propoxyphene with a rane of 0.7–13.0 mcg/ml for a serum containing 5 mcg/ml and 13 reported a range of 0.3–3.0 mcg/ml of norpropoxyphene for a serum containing 2 mcg/ml. The specimen which contained about five times the lethal concentration was identified by about only 44% of the laboratories and quantitated by about 25% with a very wide range of results. This could serve as an evaluation of the state of the art of analysis for the drug in 1978. We infer that many cases are missed because of generalized inadequacy of the laboratories.

In 1971 when the patent on propoxyphene expired, propoxyphene napsylate was introduced. It was hoped that its lower solubility would prevent poisoning of overdoses, unfortunately we have seen no evidence of this. In 1978 in North Carolina where 31 deaths were attributed to propoxyphene, the tradenames were given in the histories on 17 reports. Thirteen had the tradenames of one manufacturer; 8 were for a propoxyphene hydrochloride product and 6 were for a propoxyphene napsylate product (one case had both named).

Our attention was attracted to the drug in 1972 when we applied a specific method of analysis developed in our laboratory to specimens submitted from a number of unexplained deaths. If an adequate method of analysis for the drug had existed in 1957, it is interesting to speculate whether overdose deaths would have been detected and if they had, would the use of the drug have been discouraged. If propoxyphene were not legally available, it is our opinion that there would be no incentive to prepare the compound or to traffic in this drug for the illicit market.

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(1) Pharmacy Times, April 1973, 4, 5, 6, 7.

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(3) Miller, R. R., Propoxyphene: A Review., Am. J. Hosp. Pharm., 34: 413–423, 1977.

(4) Finkle, B. S., McCloskey, K. L., Kiplinger, G. F., and Bennett, J. F. A National Assessment of Propoxyphene in Postmortem Medicolegal Investigation, 1972–1975., J. Forensic Sci., 21: 706–742, 1976.

(5) College of American Pathologists 1977 Special Toxicology Set T–C Laboratory Survey Specimen T–14.

DAWN DEATH DATA

We have been asked to comment on DAWN death data. (1) We can only comment on material available to us. It appears that a great deal of the data is generated on "mentions" of drugs. In our experience drugs mentioned by emergency room personnel or by medical examiners which we assume have been mentioned by the patient or others may be entirely different from those found by toxicological analysis. As for the medical examiner DAWN data, it is our opinion that it is hopelessly confused in the "Drug Induced" or "Drug-Related deaths by naming drugs which may be present but may not be enough to cause death or to be a contributory cause. This is further complicated by allowing a Cause of Death Determination to be supported by factors other than "Toxicological Lab. Report" (p. 8 DAWN VI). The data would be meaningful if it was based on the cause of death as certified by the medical examiner where the determination was based on the finding of a toxicologically significant concentration of substance in the body of the deceased. Table 4.7 page 57 of DAWN VI indicates that there were 308 diazepam-induced deaths and 209 codeine-induced deaths. A national survey reported that 2 deaths of the 1239 "diazepam-related deaths" surveyed "could be substantiated as deaths resulting from the actions of diazepam and diazepam alone." (2) One of these was in Canada, the other was in the United States. In North Carolina in the past 5 years we have 2 deaths certified as diazepam deaths and 3 deaths certified as codeine deaths.

Another problem with the DAWN data is graphically illustrated in an article where codeine was blamed for "16.6 Drug-Related Deaths per Million pills" and propoxyphene was blamed for 1090 deaths or "1.6 Drug Related per Million pills." (3) We believe that there were far fewer than 420 codeine deaths. Using data generated by the same company there were 2 codeine-containing generic preparations which totaled 1,431,000 prescriptions. (4) Tylenol with codeine was ranked seventh in prescription frequency and Empirin compound with Codeine was ranked 14 with Dalmane being ranked 13. The DAWN data projects 12,795,000 Dalmane prescriptions. Estimating at least 13 million prescriptions for Tylenol with codeine and 10 million for Empirin Compound with Codeine for a total of 23 million codeine-containing prescriptions, using an estimate of 36 pills per prescription would give a total of 828 million pills or 0.5 deaths per million pills. Our projections would mean that rather than "16.6 codeine-related deaths per million pills" there would be about 1/30th that number or 0.5. It is our opinion that more than 23 million codeine prescriptions are dispensed and that less than 100 deaths are attributable to codeine. The company that produced the statistics should be able to confirm or correct our estimates.

It appears that the deaths related to codeine were attributed to codeine "pills." Most prescriptions for codeine are for tablets of codeine combined with aspirin or acetaminophen which were not included but represent about 98 percent of the codeine dispensed. Had this been done in the case of propoxyphene the 1.6 propoxyphene related deaths per million "pills" would have been about 16.

In summary the DAWN data and interpretations of it make it appear that there are many codeine deaths and that the death rate per million doses is very high and that codeine is about 10 times more lethal than propoxyphene. We find in North Carolina that there are about 75 propoxyphene deaths to one codeine death.

From the survey it has also been estimated that there are about 880 "Valium" related deaths. In our opinion deaths due to Valium are very rare and in our opinion should be 10 or less.

In the one year interval May 1976 to April 1977, 10 marihuana related deaths have been estimated. We know of no documented death due to marihuana in the United States at anytime.

REFERENCES

(1) Project Dawn VI, May 1977–April 1978, I.M.S. American Ltd. Ambler PA.

(2) Finkle, B. S. and McCloskey, K. L., The Role of Diazepam in Postmortem Medico-Legal Investigation—Center for Human Toxicology—Salt Lake City, Utah. November 1977.

(3) DAWN Data—Drug Related Deaths Tallied, U.S. Journal of Drug and Alcohol Dependence 2 :2, April 1978.

(4) 1977 Top 200 Drugs. Pharmacy Times, p. 41–48, April 1978.

OPINIONS

There are at least 1,200 deaths a year in the United States due to propoxyphene. The majority of these are suicidal overdoses from about 12 or more tablets or capsules obtained by a legal prescription. The average prescription is for about 30 dose units.

Propoxyphene was present in the majority of our cases in sufficient concentrations to cause death even if the other drugs found were not present.

Deaths would have been attributed to the drug earlier and even now more frequently if adequate toxicological analyses were available.

Determination that death is caused by a drug should only be made when sufficient concentration of the drug is found in appropriate specimens and no other adequate explanation for death is found.

Propoxyphene is a narcotic, opiate, central nervous system depressant, analgesic of questionable value.

Aspirin, acetaminophen or codeine are much safer and appear to be sufficiently effective.

Senator NELSON. Our next witness is Dr. Larry V. Lewman, forensic pathologist, Multnomah County, Oreg., medical examiner.

You are last on the panel. I am sorry you had to wait so long.

STATEMENT OF LARRY V. LEWMAN, M.D., FORENSIC PATHOLOGIST, MULTNOMAH COUNTY, OREG., MEDICAL EXAMINER

Dr. LEWMAN. My name is Larry V. Lewman; I am a physician; my specialty field of practice is forensic pathology.

My current responsibility is to investigate unexplained deaths throughout the State of Oregon, under the Oregon State Medical Examiner's Law.

I am Board certified in both anatomic and forensic pathology and my training, duties, and responsibilities similar to Dr. Hudson's.

The State of Oregon has experience, since the mid-1970's, an increase in propoxyphene deaths that could best be characterized as alarming.

It is now the No. 1 cause of drug overdose death in the State of Oregon and has been for the last 3 years.

During the past 3 years, propoxyphene deaths have equaled or exceeded the combined total of deaths from barbiturates and heroin.

The largest number of deaths attributed to this drug was 39 from July 1977 to July 1978.

There is a population of approximately 2 million in Oregon, and this represents an incidence rate of about 2 per 100,000 population.

The figure by itself does not mean much, unless you compare it with something. I will compare it with the homicide rate as everybody understands murder.

Depending where you go in the State of Oregon; the rural communities or the city of Portland, the rate of death from propoxyphene varies from between one-third to a little less than one-half the homicide rate. Slightly less than half as many people die from propoxyphene as die from homicidal violence.

Our statistics are, I think, as accurate as any in the country and far more accurate than most.

We have a Statewide medical examiner system. These deaths are investigated by physicians, and are under the statewide control of two forensic pathologists. We have a toxicology setup that is as good as any on the west coast or in the country for that matter, to chemically analyze autopsy specimens.

Manner of death simply means accident, suicide, homicide, undetermined, that is, we do not know.

The breakdown of these deaths in our State: About 60 percent I believe are accidental, the other 40 percent are about equally divided between suicides and undetermined.

If I thought most of these deaths were suicides, I would not be here beating on the table. I do not think they are.

Obviously, a person bent on destroying himself can take an overdose of almost anything.

Barbiturates remain the most common drug overdose suicide in the State; about 20 percent of propoxyphene deaths are so ruled.

This, I realize, conflicts with the large survey of propoxyphene deaths, done by the Finkle-McCloskey group in Utah.

Finkle stated 45 percent of these are suicides. I think their data is inaccurate, and I think it is inaccurate because the toxicology is incomplete.

Dr. Wolfe stated in his testimony that in only 22 of the 1,022 cases surveyed by Finkle were nor-propoxyphene levels determined.

We find the propoxyphene/nor-propoxyphene ratio vitally important in making the distinction between suicide and accident.

The majority of the propoxyphene overdoses in the State fall in the accidental category.

I believe about 60 percent are accidental deaths. Certainly some of the 20 percent ruled undetermined would also fall into the accidental category.

Of these, the majority (about 60 percent), involved propoxyphene and its metabolite as the only significant drug detected.

The other 40 percent of accidental deaths are attributed to the combined effects of propoxyphene and another agent, usually alcohol or Valium (diazepam).

The background history of these drug abusers runs the gamut of the socioeconomic spectrum. I think generally you can characterize them as low middle class to middle class.

Most of them are middle age to young middle age, 20's to 30's, we find a slight male bias.

Some of them have become addicted to the drug, while taking it for legitimate pain problems, such as on-the-job injury or a postsurgical complication of some sort.

Others have become addicted while taking the drug for its euphoric effect or psychosomatic pain.

Generally, these people do have an unstable mental history, alcoholism, multiple drug abuse, psychiatric hospitalization, and so forth.

For the most part, these are not the illicit drug abusers; not the street users of heroin.

The source of the medication in most of our deaths was legitimate physician prescription. Rarely did we find that the patient was running around to different doctors, and different pharmacies to hide his abuse.

Why? He does not need to.

Propoxyphene is a schedule IV medication under the Comprehensive Drug Abuse Prevention and Control Act. The prescription can be refilled up to five times in a 6-month period without the physician being further consulted.

Senator NELSON. The prescription would include how many tablets?

Dr. LEWMAN. It is not limited to my knowledge.

Senator NELSON. So then you are saying the doctor may give a prescription which may be renewed five times, with the doctor deciding how many tablets would be included in each prescription?

Dr. LEWMAN. That is right, and have no knowledge of when or if it is refilled. We have 30 to 34 million prescriptions a year for this drug that can potentially be refilled up to five times.

That I submit has a potential for a lot of abuse. Why do I think most of these deaths are accidental?

First, I want to state I have not seen a case of anybody dying from this drug when it is taken as recommended. The real nitty-gritty of this problem, I think, is that these are accidental deaths, and this results from the breakdown product of the drug.

After propoxyphene is taken, it is broken by the liver, into a series of compounds, which we will refer to as metabolites, or breakdown products, and the most significant of these is nor-propoxyphene.

Nor-propoxyphene is significant because of its long half-life. It has about a 40-hour half-life. The parent drug, propoxyphene, has a life of about 8, 10, 12 hours. If a patient has taken several of these pills every 4 to 6 hours, the parent drug (propoxyphene) is being rapidly broken down. The nor-propoxyphene metabolite, however, is accumulating for almost 2 days and eventually can reach toxic or lethal levels.

The metabolite problem is not addressed in the package insert data and there is a minimum amount of information in the literature. I am certain that prescribing physicians and the patients taking it are unaware of the significance of this toxic metabolite.

I do not think the propoxyphene deaths, in fact, I am sure they are not unique to the State of Oregon.

I will echo Dr. McBay's and Dr. Hudson's comments about Valium deaths and codeine deaths.

I have seen a handful of codeine deaths. I have never seen an overdose of Valium alone in years of investigating drug deaths.

I am sure it could happen, but I have not seen one.

I feel the data is wrong in that respect but I think the most significant thing about the DAWN data is that it does not reflect the majority of the country.

We have to remember that death investigation systems, in most States in this country, remain in an abysmal state.

In many States of this country, you still have an elected coroner system, which means you have funeral directors, gas jockeys, police officers, district attorneys, and so forth, anyone that can get 50 percent of the votes plus one, running around investigating deaths.

These people are simply not trained, they do not have the investigative background, they do not have the technical apparatus to accurately diagnose and report these deaths.

It is a complex investigational problem, and much of the country is simply not yet adequate to the task.

All I can do is estimate. I think we probably have 3,000 to 4,000 propoxyphene deaths in the United States every year. I arrive at this figure by simple taking the statistics from the good sound death in-

vestigation systems such as North Carolina and Oregon statewide, and local systems such as San Francisco, Phoenix, and Dallas.

Apply our incidence figures nationwide and you probably have 3,000 to 4,000 deaths annually.

EDUCATION HAS DECREASED THESE DEATHS IN OREGON

Last year during April we had eight propoxyphene deaths in a period of 2 weeks in the Portland area alone.

This led to a media blitz. I appeared on television several times. So did my partner. Editorials were printed in the newspapers, locally and statewide. Information was disseminated to physicians throughout the State and the numbers have dropped drastically.

From July 1977 to January 1978, we had 18 propoxyphene deaths. From January to July 1978 we had 21.

After this media blitz, we had eight in the last half of the year.

I think we have demonstrated that education of the physicians and the public can decrease these deaths, but I view this as a temporary reduction.

I might add that I am frustrated on the Federal level.

I am not here to cast stones at Eli Lilly. I have found they have shown more interest and concern about the problem than the FDA.

I wrote to the FDA, May of last year. I have not as yet received an acknowledgment of my letter. I do not think the mail is that slow.

MY RECOMMENDATIONS

I am not addressing myself to banning this medication. I think that there has to be a balance between the therapeutic benefit and the obvious danger. Depending on which study you read, it is less than, equal to, or better than aspirin. I do not intend to address myself to that problem, I think it has already been adequately covered.

I do, however, firmly and unequivocably recommend propoxyphene be transferred to a schedule II drug under the Controlled Substances Act.

The case for this to me is absolutely irrefutable. It is an uncontrolled narcotic. It has the abuse potential of a narcotic, the withdrawal symptoms of a narcotic, and the addiction problem of a narcotic. In every sense of the word, it is a narcotic. And yet if you look already at schedule II narcotic preparations such as codeine, demerol, dilaudid, deaths from propoxyphene outnumber deaths from these other narcotics by a factor of multiple times; no comparison.

Transferring propoxyphene to schedule II would go a long way toward alerting physicians and patients alike to its dangers; it would at least somewhat prevent the indiscriminate refilling; it would require written prescriptions and place strict controls over the manufacture and distribution of this drug.

SUMMARY

I think this is probably the No. 1 cause of prescription drug overdose in the United States today.

It is unquestionably the No. 1 cause of prescription drug overdose in Oregon by a wide margin.

By this time tomorrow, 10 more U.S. citizens will have died from propoxyphene overdose and most of these will have been preventable accidents. I think the time has come to put a stop to it.

Thank you.

Senator NELSON. So it is your conclusion after looking at what you conclude to be the best statistical evaluations—in North Carolina, San Francisco, and Oregon—that in fact a substantial percentage, a majority of deaths, are accidental and not intentional?

Dr. LEWMAN. I believe they are in my jurisdiction.

Dr. Hudson apparently does not think so. We have not compared toxicological data.

In my cases: First we look at the background history of the patient, is there an empty bottle of pills filled 2 hours ago or is there not.

The toxicologic data is very significant. We find a high nor-propoxyphene/propoxyphene ratio and low stomach (gastric) totals in accidental cases. If we look at the suicide cases, we find a large amount of propoxyphene in the stomach. This indicates the individual has ingested a large amount of medication at once.

In suicide cases, we find a higher ratio of propoxyphene to norpropoxyphene. So I do not reach this conclusion just on toxicology, but on the entire spectrum of the investigation of the death.

Senator NELSON. Do you see any inconsistency in having methadone listed on schedule II and propoxyphene not?

Dr. LEWMAN. Oh, absolutely.

I think I have had two cases of methadone deaths in the last year.

You can say this about any of the narcotics in schedule II. Propoxyphene is hands down by a multiple of several times more common as a cause of drug overdose death than any of them.

Senator NELSON. And how is propoxyphene related to methadone?

Dr. LEWMAN. It is chemically very similar.

I could not draw the structure. Dr. McBay could probably address himself to that question better than I.

They are chemically very similar. They are both narcotics.

Senator NELSON. Thank you very much for your testimony. We appreciate the time that all of you have taken from your busy work to come here to testify on this important subject, and if you have any additional material you wish to submit, the record will be open for another 2 weeks.

Senator LEVIN. Mr. Chairman, I wonder in that regard, if we could have comments, either now briefly or in writing, as to your duty and responsibility of your profession, I gather in future hearings we will be hearing from Lilly as to their defense, and so forth, but one of the most striking things in the hearings this morning is apparently the inadequacy of the professional defense that is perceived by the four obviously qualified people is a problem.

I know this is not the purpose of the hearing, whether we could have some thought addressed to that, I think the first line of defense probably is the profession against this kind of problem, the Government is slow to act, and I am just wondering if there are any brief thoughts, it is kind of late for this, but perhaps later in writing, you gentlemen could give us some brief thoughts.

Senator NELSON. Fine.

Anybody wish to comment on it at this moment?

Senator LEVIN. To put it more sharply, are your views shared by your colleagues, in your various areas of expertise, who have had the kind of background that you have had and done this kind of research that you have done?

Dr. LEWMAN. In the field of forensic pathology, yes.

Dr. MOERTEL. I think in the field of clinical pharmacology, my views are shared by those knowledgeable in research studies of analgesics.

I do feel that there is a problem in education, and I wish I knew the answer to that, Senator.

I think it is very important but the problem is that as we survey the physicians who prescribe drugs, we find that most of their education is achieved through the drug companies themselves, the detail man being the most effective educator. When we get to the other education media, they really do not have as strong an impact on the physician as we would like them to have.

I agree there is a problem here.

How you address the problem I think is very difficult.

I do not know the answer to that.

Dr. HUDSON. To the same point, between the efficacy of drugs, and the frequency with which they are used, it is not very good.

There are some drugs that are not so popular, and others that are, and we are talking about what has been referred to as part of advertising, and partly of whatever it is that captures people's imagination as far as things inducing them to purchase or to prescribe medication.

Senator NELSON. Your observations in response to Senator Levin's question are the same as the responses we have gotten over a period of 11 years from distinguished pharmacologists who have been asked that kind of question, and the same as the findings of various studies that have been done respecting the prescribing practices of physicians.

Thank you very much. I appreciate your taking the time to testify.

Dr. LEWMAN. Thank you.

[The prepared statement of Dr. Lewman follows:]

STATEMENT OF LARRY V. LEWMAN, M.D., FORENSIC PATHOLOGIST, MULTNOMAH COUNTY, OREG., MEDICAL EXAMINER

PROPOXYPHENE-RELATED DEATHS IN OREGON

HISTORY OF PROPOXYPHENE-RELATED DEATHS IN OREGON

There has been an alarming increase in the number of propoxyphene-related deaths in the state of Oregon since the mid-1970's. Propoxyphene was by far the number one cause of fatal drug overdose in the state during 1976, 1977 and 1978; and the numbers have been on the increase until the latter half of 1978. The statistical increase is best reflected by comparison with the other most common agents causing drug overdose deaths, namely barbiturates and intravenous narcotics (heroin). During 1975, propoxyphene-related deaths approximately equalled deaths from the barbiturate group, and deaths from intravenous narcotics outdistanced both by a factor of about 1.5 to 1. During 1976 and 1977, propoxyphene deaths approximately equalled the combined total of narcotics and barbiturate deaths during both years. The computer print-out for 1978 has not yet been completed, but it is my impression that propoxyphene-related deaths exceeded the combined totals of narcotics and barbiturate deaths by a wide margin this past year.

THE NUMBERS IN PERSPECTIVE

The largest number of propoxyphene-related deaths in any year in Oregon was thirty-nine (39), occurring during fiscal July 1977 to 1978. The population of the state is approximately 2,000,000 representing an incidence rate of 2 per 100,000 population. This is approximately one-third the homicide rate for the state.

Multnomah County includes the city of Portland and is the state's largest metropolitan area. The incidence of fatal propoxyphene abuse in Multnomah County is greater than the state at large. During the July 1977 to July 1978 year, almost one-half as many individuals died propoxyphene-related deaths as succumbed to homicidal violence.

DEATH INVESTIGATION IN OREGON

Oregon has a state-wide Medical Examiner System responsible for the investigation of violent and unexplained deaths throughout the state. This is in contradistinction to states retaining an elective coroner system in which frequently unqualified and untrained individuals are responsible for directing the death investigation program in an individual county.

Each Oregon county has an appointed trained physician responsible for the investigation of violent and unexplained deaths in that county. The program is under the state-wide control of two Board Certified Forensic Pathalogists in Portland. All Medical Examiner cases are reviewed by one of the state pathologists.

Suspected drug-related deaths fall under the State Medical Examiner's Law and must be investigated by the physician-medical examiner in charge. This is true whether the death occurs at home or in a hospital. The medical examiner or his trained deputy visits the death scene, obtains a history, seizes medication and backchecks prescription dates, number of pills, etc., with the prescribing physician and the pharmacy. A complete postmortem examination is conducted by a certified pathologist and body tissues and fluids obtained for toxicologic analysis.

Drug analyses are done by the Department of Toxicology at the University of Oregon Medical School, under the direction of Dr. Jack Aitchison, a Forensic Toxicologist. The laboratory is equipped with the most advanced instrumentation, including a gas chromatograph/mass spectrograph set-up. Only a handful of laboratories on the west coast possess this degree of sophisticated instrumentation.

Following the completion of the background investigation, autopsy and toxicology studies, the medical examiner comes to a conclusion about the cause and manner of death and signs the death certificate.

SUICIDE, ACCIDENT OR UNDETERMINED?

Most fatal propoxyphene overdoses fall into three categories, and I will discuss each briefly in light of my experience as a Forensic Pathologist and Medical Examiner in Oregon.

Suicides.—Obviously, a person bent on destroying himself can take an overdose of almost anything. The short-acting barbiturates remain the drugs of choice in most suicides in Oregon, and deliberate self-destruction by propoxyphene is not common. I realize this conflicts with the Journal of Forensic Sciences article, Volume 21, No. 4 by Finkle-McCloskey, et al., in which they surveyed propoxyphene deaths from several jurisdictions and concluded that approximately 45 percent of these overdoses were of suicidal manner. I believe this conclusion is inaccurate because of incomplete toxicologic data. Propoxyphene is broken down to norpropoxyphene by the liver. The authors surveyed one thousand twenty-two (1,022) propoxyphene-related deaths, and the concentration of norpropoxyphene in the tissues was determined in only twenty-two. Experience in Oregon suggests that the relative concentrations of norpropoxyphene and propoxyphene in the tissues is of vital importance in distinguishing between suicidal and accidental manner of death. Between 20 and 25 percent of propoxyphene-related deaths are considered suicides. An approximately equal percentage of propoxyphene-related deaths were signed as "manner undetermined." This simply means that following thorough investigation, autopsy and toxicologic examination, the medical examiner was unable to determine whether the death represented an intentional act or an accidental overdose.

Propoxyphene in combination with other compounds.—As in most studies, propoxyphene-related deaths in Oregon commonly involve other compounds, most commonly ethanol, diazepam, and a wide variety of others. When it is felt that another chemical agent contributed along with propoxyphene to the death, the death is attributed to the combined effects of propoxyphene and the other agent or agents, and is so indicated on the death certificate. If propoxyphene is the only drug detected in significant quantities and other agents are either absent or felt to be insignificant in their concentrations, death is attributed to propoxyphene alone.

Of the propoxyphene-related deaths ruled either accidental or undetermined manner, approximately 60% represented deaths from propoxyphene alone. The remaining 40% resulted from the combined effects of propoxyphene and other agents, most commonly ethanol or diazepam (Valium).

Accidental overdoses of propoxyphene.—It is this category into which most of the propoxyphene overdoses in Oregon appear to fall. About two-thirds (⅔'s) of propoxyphene-related deaths are determined to be accidental. Of these, the majority involve propoxyphene and its metabolite as the only significant compounds detected on thorough toxicologic screening.

BACKGROUND HISTORY OF ABUSERS

The cases in Oregon run the gamut of the sociologic and socioeconomic spectrum. Most involve deaths of individuals in their 20's or 30's with a slight male bias. A few were offspring or spouse of physicians and professionals; some become clearly addicted to the medication while using it for a legitimate variety of pain problems such as on-the-job injury or surgical complications. Others became addicted while using the drug for pain of psychosomatic origin or for its euphoric effect.

In the majority of instances, examination of the individuals' background elicited an unstable mental history and, in many cases, a pattern of multiple drug abuse, psychiatric hospitalization, alcoholism, and the like. A few has a history of intravenous narcotism at some time during their life. For the most part, however, propoxyphene abusers are not the illicit drug abusers prone to use heroin or "street drugs."

SOURCE OF MEDICATION

In the large majority of cases, propoxyphene was obtained by legitimate physician prescription. Eli Lilly's Darvon products were the medications most often obtained. In a few instances, deceased individuals obtained drugs from different physicians and frequented different pharmacies in an attempt to hide their abuse. More commonly, the drug was obtained from a single physician and a single pharmacy. We should remember that propoxyphene is a Schedule IV medication under the Comprehensive Drug Abuse Prevention and Control Act of 1970. This enables the patient to refill an oral prescription up to five times during a six-month period without the knowledge of his physician.

Illicitly-manufactured propoxyphene is not a significant problem in Oregon. It is rare that the source of the drug was an "on the street" purchase. Commercial bottles or propoxyphene were discovered in a handful of cases and were likely obtained in pharmacy burglaries. In each of these instances, the deceased individual has a strong history of multiple drug abuse and usually a heroin habit.

WHY THE ALARMING NUMBER OF ACCIDENTAL DEATHS FROM THIS DRUG?

It should be noted that I have yet to see a case of accidental death from this drug when taken as recommended, i.e., 65-100 mg every 4–6 hours. In every instance, the deceased has taken more than the recommended amount of medication, though the repetitive nature in which it is taken prohibits me answering the question "How much is too much?"

In my opinion, these accidental deaths result not from propoxyphene itself, but from its metabolic breakdown product. Propoxyphene is broken down to a variety of compounds by the liver, the most significant of which is nor-propoxyphene. The crux of the problem is the largely-unrecognized toxicity of the nor-propoxyphene metabolite and its prolonged retention in the body. Finkle's study alluded to the fact that nor-propoxyphene may be toxicologically more important in many cases than the parent drug. In Finkle's survey, the level of nor-propoxyphene was determined in a miniscule percentage of cases, and the authors cited

the lack of nor-propoxyphene toxicity data as a problem in analyzing the effects of this drug.

Nor-propoxyphene is toxicologically significant because of its prolonged retention. Nor-propoxyphene has a half-life in the body of about 38–40 hours. This is between three and four times the half-life of the parent drug, propoxyphene. As the patient takes the drug every few hours, the desired effect, whether it be euphoria or pain relief, is dissipated in the first several hours. The propoxyphene is being rapidly metabolized while the toxic nor-propoxyphene metabolite is constantly building up because of its long half-life.

Accidental propoxyphene overdoses in Oregon consistently reflect nor-propoxyphene levels between 2–10 times propoxyphene levels. In accidental deaths, total gastric (stomach content) levels are generally low, indicating that a large amount of drug was probably not ingested at once. These results are in contradistinction to the suicide case in which we find higher blood propoxyphene/nor-propoxyphene ratios and a large amount of propoxyphene in the stomach.

REPORTED DEATHS ARE A SMALL PERCENTAGE

Large numbers of propoxyphene deaths are not unique to the state of Oregon in 1978. There is no question in my mind that the 589 propoxyphene-related deaths reported through the DAWN network in 1977 represents but a small percentage of the deaths from this drug nationwide.

It should be recognized that medical-legal death investigation systems in most states in this country remain in an abysmal state. Many states and communities still operate under an elected coroner system which results in a wide variety of untrained individuals attempting to investigate all types of unexplained death. For example: In one neighboring state, elected coroners include a newspaper editor, funeral directors, ambulance attendants and prosecuting attorneys. Each of these individuals is responsible for directing the death investigation program in his or her particular county, and that authority is autonomous. Not only are they inadequately trained to investigate such deaths, but they do not have access to the sophisticated instrumentation required to do drug analyses; and autopsies are done on an infrequent and inconsistent basis, depending upon the coroner's budget, whims and training. I can guess at how many propoxyphene-related deaths occur in communities with such a set-up, and this constitutes much of the nation. Suffice to say, many are missed.

I would estimate that there are about 3,000 to 4,000 propoxyphene-related deaths annually in the United States. I arrive at this estimate by taking incidence figures from sound and well-run state-wide medical examiner systems such as North Carolina and Oregon and local jurisdictions such as Dallas, Phoenix, Miami and San Francisco. There are, of course, others.

PUBLIC AND PHYSICIAN EDUCATION HAS DECREASED PROPOXYPHENE-RELATED DEATHS IN OREGON

During the past few years, the Oregon State Medical Examiner's Office has attempted, on an episodic basis, to alert the public and physicians to the dangers of this medication through press coverage and publications to physicians. The dramatic increase in these deaths early last year, including eight in a two-week period in Portland, prompted a "media blitz." Several articles appeared in newspapers throughout the state, and some of this attained nationwide attention. I appeared on several local television news shows and talk shows and recorded radio interviews throughout Oregon and in some neighboring states. Information was disseminated to Oregon physicians through the State Medical Examiner's Newsletter and the Oregon State Health Division's Communicable Disease Summary. The state recorded eight propoxyphene-related deaths during the six months following this "blitz." This is in contrast to the two preceding six-month periods in which the state recorded 21 and 18 propoxyphene-related deaths respectively.

I feel we have demonstrated that public and physician education can help decrease the numbers of these deaths, but this is not the answer to the problem. I expect the decrease to be temporary and the problem to recur as the publicity subsides. I view widespread publicity as a short-term deterrent with some long-range beneficial effect in educating the physician-prescribing community.

Oregon's attempts at bringing the attention of the federal government to this problem have met with frustration. My letters to two officials of the FDA written

in early May have yet to meet with any response whatsoever. Oregon State Health Officer, Dr. Ed Press, has similarly petitioned the FDA for reclassification of propoxyphene in November, 1978.

IMMEDIATE RECOMMENDATION

I do not intend to address in any detail the proposed ban of propoxyphene. A decision on banning any medication must be based both upon its potential hazard to the community and its therapeutic benefit to those not abusing it. My role is limited to the investigation of deaths involving propoxyphene. I don't prescribe it; I rarely have an opportunity to evaluate its therapeutic benefit. Though I am aware there are several studies indicating that propoxyphene is of limited value as an analgesic, testimony to that effect must come from others more directly involved with its clinical effects. If it is determined that this drug is of no therapeutic benefit as a pain reliever, it should be banned.

I firmly and without reservation suggest that propoxyphene be reclassified as a Schedule II drug. There can be no question but that propoxyphene is a narcotic, acts like a narcotic and has the abuse and addiction potential of a narcotic. Propoxyphene-related deaths outnumber deaths from other narcotic compounds such as Demerol, Dilaudid, Codeine, Percodan, Methadone and others by a multiple of several times. Most of these other narcotics are already Schedule II preparations. Placing propoxyphene under Schedule II controls would help alert physicians and patients to its danger, prevent indiscriminate refilling, require a written prescription, and in general place much more strict controls on the manufacture and prescribing of this medication.

SUMMARY COMMENTS

Propoxyphene is probably the number one cause of drug overdose in the United States today. The investigation and detection of these deaths is a complicated problem; and many, if not most, death investigation systems in this country are inadequate to this task from the standpoint of personnel, training and instrumentation. Unquestionably, many propoxyphene-related deaths are not recorded.

Propoxyphene is definitely the number one cause of drug overdose in the state of Oregon by a wide margin, surpassing the combined total of deaths from heroin and barbiturates. Data from the best death investigation systems in this country, for the most part give similar results. By this time tomorrow, about ten more U.S. citizens will have died from the effects of propoxyphene, and most of these will have been preventable accidents. The time has long since come to put a stop to it.

Senator NELSON. Our final witness this morning is Mr. Kenneth A. Durrin, Director, Office of Compliance and Regulatory Affairs of the Drug Enforcement Administration, and he is accompanied by Mr. Donald E. Miller, Chief Counsel.

STATEMENT OF KENNETH A. DURRIN, DIRECTOR, OFFICE OF COMPLIANCE AND REGULATORY AFFAIRS OF THE DRUG ENFORCEMENT ADMINISTRATION, ACCOMPANIED BY DONALD E. MILLER, CHIEF COUNSEL

Mr. DURRIN. Mr. Chairman, members of the committee, gentlemen, I am very pleased to be here representing the Drug Enforcement Administration.

Accompanying me is Mr. Donald Miller, Chief Counsel of DEA.

Mr. Bensinger asked me to convey to you, Mr. Chairman, his regret that he could not be here personally, and he also asked me to commend you and your committee for holding this kind of hearing on propoxyphene.

In our deliberations in response to the petitions we have received from the Health Research Group, and from the State of Oregon, we

certainly will be taking full vantage of the results emanating from your hearings and from your deliberations.

In 1978, of the 1.4 billion prescriptions dispensed in retail pharmacies, 31.2 million were for products which contained propoxyphene. In this country, 59 companies now market approximately 150 products which contain propoxyphene alone or on combination with other substances.

Propoxyphene is an abused drug and its abuse can and does lead to physical dependence, and you have heard testimony that it is perhaps half as effective as codeine. DEA needs to identify and evaluate the scope and extent of drug abuse in the United States. DAWN, the Drug Abuse Warning Network is one of the major indicators of drug abuse in this area. There have been a number of comments on the Drug Abuse Warning Network, and I would like to say that we are in our seventh year with this system, which when taken into proper context as an indicator system, has proven to be very valuable in terms of showing what the current situation is in the 24 cities which are reporting.

I will comment on that a little more later in my testimony in terms of the earlier comments here.

Now, in the DAWN program, the emergency room mentions relative to all drug mentions in DAWN has remained essentially constant over the past 3 years, ranging from 2.4 percent in 1975 to 2.2 percent of all drug mentions in 1978.

In terms of frequency of being noted in emergency room reports, propoxyphene ranked seventh in 1975, 1976, and 1977.

The next year, 1978, propoxyphene ranked eighth because phencyclidine came into more prominence.

Propoxyphene ranks third behind heroin and alcohol in combination with other drugs in terms of drugs associated with death in DAWN ME reports.

This confirms comments here this morning, indicating that propoxyphene was the highest cause of death among legitimate drugs.

Based on information received since January 1975 from medical examiners who have consistently reported to DAWN, the number of propoxyphene-related deaths is as follows: 1975, 502; 1976, 429; and 1977, 598.

It will be 6 to 9 months before we have complete data from medical examiners regarding deaths in calendar year 1978.

This data incidently is updated monthly based upon reports in from the medical examiners; however, because of the lagtime, it does take a good 6 to 9 months.

The data we have, as I have indicated, through the end of 1977, indicates the problem has remained at a high constant level through that time, and the first 3 months of 1978 continues to remain at that high level.

Senator NELSON. Did you hear Dr. Wolfe's testimony?

Mr. DURRIN. I certainly did.

Senator NELSON. Did you agree with that?

Mr. DURRIN. Yes; I do.

Senator NELSON. Does it take some months into the next year to get the statistics of the final quarter?

Mr. DURRIN. Yes; we worked closely with Dr. Wolfe and his staff in terms of furnishing them with information.

According to DAWN ER reports, suicide is the motivation behind 56 percent of the incidents. Psychic effect accounts for 13 percent; dependence accounts for another 5 percent of the reasons for propoxyphene abuse.

In the remaining 26 percent of the cases, DAWN does not record a specific motivation.

According to DAWN ME mentions, the following were recorded as the manner of death:

	Percent
Suicide	44
Accidental (unintentional overdose) motivation for taking drug unknown	22
Accidental (unintentional overdose) motivation for taking drug psychic effect or dependence	13
Undetermined	21

In looking at this data, it tends to confirm another comment made earlier that there are a large number of persons who are accidentally killing themselves, using propoxyphene alone, or in combination.

How is propoxyphene obtained?

Based upon the DAWN emergency room data, legitimate prescriptions are used at least 58 percent of the time.

This contrasts sharply with 1 percent reported as obtained through a street buy, or the 4 percent obtained through other illegal activity such as theft and forged prescriptions.

In other words, we have here a product which patients are obtaining through legal prescriptions, and then are having toxicity problems with it.

Now, with regard to scheduling drugs, drugs are placed in schedule II, or a lower schedule according to their abuse potential and currently accepted medical use.

For schedule II, the criteria are currently accepted medical use and high abuse potential with severe psychic or physical dependence liability. Each succeeding schedule requires a lesser potential than is reflected for schedule II and a lesser degree of dependence liability.

Now, with regard to propoxyphene, despite the fact it is a highly toxic drug, as a matter of fact, the highest toxic drug in terms of contributing to deaths of legitimate drugs in the United States, it has not in the past indicated a high abuse potential, or a severe dependence liability.

In other words, a drug can be highly toxic without possessing those factors.

The issue of severity of abuse potential and the addiction liability of propoxyphene, compared to morphine-like drugs, has been discussed and reviewed by experts in the field, over a period of several years.

The 1957 findings of Drs. Fraser and Isbell of the Public Health Service Center that, "(propoxyphene's) overall addiction liability is estimated to be no greater, and is probably less, than that of codeine" were repeatedly confirmed.

In 1973, DEA first proposed to HEW that propoxyphene be placed under control. HEW did not feel control was warranted at that time, but that we should continue to monitor the drug.

In March 1976, DEA submitted updated information to HEW regarding the abuse of propoxyphene.

The ensuing deliberations resulted in HEW's recommendation to control propoxyphene in schedule IV, and DEA controlled the drug effective March 14, 1977.

Senator NELSON. Let me back up.

What did you say in comparing codeine with propoxyphene?

Mr. DURRIN. Drs. Fraser and Isbell stated, and this is a quote "(propoxyphene's) overall addiction liability is estimated to be no greater, and is probably less, than that of codeine."

Senator NELSON. In your judgment, from your experience, would you agree with that statement?

Mr. DURRIN. Yes, I would, sir.

Again, I am not a medical expert, I am a regulator, but I would.

Senator NELSON. If that is correct, would you believe that propoxyphene ought to be on schedule II as is codeine?

Mr. DURRIN. No; codeine was placed on schedule II as a result of the international convention, and when the Controlled Substances Act was passed, it was placed on that schedule to conform to the treaty; but I might point out that only about 3.5 percent of the codeine dispensed for medical purposes in the United States is in schedule II products.

About 75 percent of the codeine is in combination products in schedule III and another 10 percent is in the codeine cough syrups in schedule V.

The bulk of the legitimate codeine products in the United States are on a lesser schedule, which I feel is appropriate.

The Public Citizens Health Research Group and the Oregon Department of Human Resources have petitioned to place propoxyphene in schedule II.

In response to these petitions, DEA has undertaken a survey to update information on the abuse of propoxyphene. Data regarding the nature and extent of propoxyphene-related unlawful or unprofessional activities has been solicited from each State government.

Data is being assembled from several other sources: DAWN, DEA lab analysis of evidenciary exhibits, DEA enforcement case files, compliance investigations, theft reports and the scientific and medical literature.

I anticipate that this information will be assembled and evaluated by early spring of this year.

Shortly thereafter, these findings will be submitted to HEW for its evaluation of the medical and scientific issues associated with the petition for rescheduling.

Since criteria for scheduling is largely based on potential for abuse and the severity of psychological or physiological dependence, I think that it may be valuable to use the available abuse data to compare propoxyphene with other drugs in schedules II and IV.

In terms of the DAWN ME mentions per million prescriptions dispensed in retail pharmacies, propoxyphene falls in the same general class as codeine, meprobamate, diazepam, and amitriptyline.

The schedule II drugs responsible for a substantial portion of the DAWN ME mentions, are implicated in deaths at least 10 times more frequently than propoxyphene.

For example:

Pentobarbital—178 mentions per million Rx.

Amobarbital—416 mentions per million Rx.

These figures are contrasted with propoxyphene which is implicated in 15 deaths per million prescriptions dispensed.

I want to emphasize that this does not show the complete picture.

One of the biggest problems, and it has been alluded to here this morning is that with propoxyphene, unlike some of these other drugs, it is regarded by many of the medical profession in my judgment, and by patients as well, as a relatively innocuous drug in terms of relative possibility of harm, and it has proven to be, according to the data and according to the testimony you have heard here this morning, far from a harmless substance.

A significant question, and one that has a bearing on the outcome of the pending petitions, is "Has placing propoxyphene in schedule IV as of March 1977 had an impact on its abuse?"

With respect to DAWN ER mentions, I can point to a statistically significant decrease since that time.

At this point there is insufficient data for DAWN ME reports to make a comparable claim for ME mentions.

It will be another 6 to 9 months before that data is complete for 1978.

For medical examiners mentions, from January 1975 to February 1977, they average about 40 a month, and from April 1977 through December of 1977, which is as far as we can go at this point, they average about 42 mentions a month, and as I indicated, during the first 3 months of 1978, they are running about the same level.

With regard to propoxyphene, the number of thefts are very slight compared with some of the other drugs that we have under control.

It just does not appear to be a product that is preferred by thieves. This is in sharp contrast to the well-orchestrated attempts to divert such drugs as the amphetamines, phenmetrazine, the barbiturates, methaqualone, methadone, and hydromorphone, all schedule II substances. Fraudulent prescriptions and illegal dispersing are not problems with propoxyphene as they are with the drugs I just noted, although there are some problems with propoxyphene in that area. Regardless of what I have just said, the Drug Enforcement Administration is most concerned about the abuse of propoxyphene. The sizable number of deaths alone is cause for constant monitoring and interest in this problem.

The toxicity problem with propoxyphene is very real.

The Drug Enforcement Administration feels consideration should be given to several possible options in order to determine the best means of addressing the toxicity problem.

The petitions set forth two of these: Removal of propoxyphene from the market or placement in schedule II. The questions of medical usefulness of propoxyphene and the need for its continued marketing are determinations for HEW and the FDA, and DEA does not presume to venture into that area.

As to rescheduling, under the provisions of the CSA, DEA has moved into schedule II substances that we believe had a high popularity among abusers and which are available on the streets in significant quantities.

I just mentioned several of those. We will be looking for data of a similar nature, to determine whether propoxyphene meets schedule II criteria.

In addition, HEW's recommendation is required as part of the scheduling process.

At this point in time, Mr. Chairman, I do not want to prejudice data yet to come in, but it is our preliminary conclusion, that it is questionable whether the data we are gathering will support the criteria required by law for the placement of propoxyphene in schedule II; that is, a high level of abuse as contrasted with other drugs, and a severe dependence liability. Even though propoxyphene is the leading cause of deaths among legitimate drugs, it does not, according to our preliminary information, reflect such a high level of abuse or a severe dependence of liability.

However, even though this is likely to be the case, the very significant toxicity problem cannot be ignored.

If Congress wishes to move Darvon to schedule II an amendment to the Controlled Substances Act, which of course would not require meeting the legal criteria, would probably be necessary.

If Congress decides to explore this, they will be supported by the DEA.

Now, schedule II would have an impact on the quantity of propoxyphene dispensed and hence there would be less available to cause the toxicity problems.

There would be no refills.

Senator NELSON. Your responsibility is not to make a judgment as to whether it is an effective drug for the purpose it is used, or whether it has any significant medical therapeutic effect on the function?

Mr. DURRIN. That is correct.

Senator NELSON. So the testimony of Dr. Moertel, and all of the others, in particular about the studies done to show it is less effective than ordinary over-the-counter drugs, over-the-counter drugs having fewer side effects, is not a factor that you take into consideration?

Mr. DURRIN. That is correct. We defer to the FDA, HEW for the medical and scientific judgment.

Incidentally, on that score, as I indicated in connection with our response to go to the petitions, we have been canvassing State officials for information on propoxyphene in their States, and I had a response from one State where the official indicated that the problem, one of the major problems in regard to propoxyphene was because medicare patients cannot receive a payment for aspirin, which would be the drug of choice in many instances, so they are getting prescriptions for propoxyphene, with whatever toxicity problems that may result because propoxyphene is reimbursable under medicaid in that State and aspirin is not. I think that is a sorry commentary.

Schedule II, as I said, would have an impact on the quantity of propoxyphene dispensed, and no refills would significantly cut down on the dispersing of propoxyphene. There is also the psychological impact of schedule II as seen with substances we have placed there. Many prescribers prefer to write for a lesser scheduled drug, and, of course, there is also the practical factor that prescriptions must be in writing and no telephone prescriptions would be allowed. However, even though there would be a lessening in terms of the prescribing of the product: the majority of the propoxyphene mentions center around legitimate prescriptions as already mentioned here this morning by others.

While schedule II prescriptions are not refillable, an average propoxyphene prescription is roughly 40 dosage units, and the experts tell us it takes approximately 20 dosage units to cause death, probably less in combination with alcohol or with other drugs. So that even though we feel based upon our experience, there would definitely be a lessening in terms of the number of units of propoxyphene dispensed in the United States, toxicity would still continue to be a serious problem with this drug, even though it were on schedule II. The main impact and thrust of schedule II, is to prevent diversion of drugs that are in high demand by abusers, and with this particular product, the problem is the patients who obtain the drug legitimately and end up having problems with it, either intentionally or unintentionally.

If the Food and Drug Administration and HEW determine that removal from the market is not appropriate, it seems to us that there are additional options within FDA's purview over drug usage which directly address the toxicity problem.

These include:

A labeling change, perhaps a boxed warning, which would strengthen the warning to physicians of the toxicity problem and of the use of the drug in suicides.

A curtailment of the indications for use which would limit the drug's use to those conditions where it is clearly superior to other less toxic substances.

Discouragement of use, again through a labeling change, for the chronic, long term conditions which would necessitate that the patient continually have sizable quantities of the drug on hand.

Finally, a patient package insert which would warn the patient of the drug's dangers.

Only the Food and Drug Administration can pass upon the viability of these suggestions. Certainly, a review of propoxyphene's potency, efficacy, and risk-benefit ratio by FDA's medical experts is in order in light of the questions raised in the petition by Dr. Wolfe and the Public Citizen Health Research Group.

In support of this, the Drug Enforcement Administration will provide appropriate data to the FDA.

Mr. Chairman, whatever the mechanism, it is imperative that every effort be made to substantially reduce the number of propoxyphene-related deaths. The Drug Enforcement Administration will work to this end.

Senator NELSON. Any questions?

Senator LEVIN. You indicated you would support a move in Congress to consider the movement to schedule II?

Mr. DURRIN. Yes, sir.

Senator LEVIN. Have you recommended such a bill be introduced?

Mr. DURRIN. No; we have not, sir.

Senator LEVIN. Why is that?

Mr. DURRIN. Well, basically, it is an extraordinary procedure that would not normally be part of our process in terms of a drug.

The type of problem with this drug is not essentially a drug abuse problem in the usual sense.

It is a toxicology problem, and normally, that is addressed by HEW.

We have certainly monitored the deaths, and we of course furnished Dr. Wolfe information on deaths, in connection with his petitions, but that is not primarily a DEA area of responsibility.

Mr. MILLER. Could I elaborate on this?

We still have to wade through a great deal of difficulty in determining what constitutes a high potential for abuse, and what constitutes a severe dependence liability.

We know that Darvon is killing people, it is unsafe, insofar as some users are concerned.

Whether that constitutes high potential for abuse, we still have to receive evidence on this.

We have our people on the streets trying to determine whether it really has a high abuse potential, or whether it is something lower, which would disqualify it from going into schedule II.

Senator LEVIN. Is that something defined by the law or in the regulations?

Mr. MILLER. We are held to this by the law.

We have the criteria in order to put it into schedule II, it must have a high potential for abuse.

Senator LEVIN. Is the definition of high potential for abuse in the regulation?

Mr. MILLER. There is no definition. We work it on a case-by-case basis, depending on the drug.

We have never been able to come up with satisfactory regulations on it.

We rely to a great extent on the legislative history, but basically, it comes down to the evidence itself, the extent the drug is used, and the witnesses themselves that appear at the administrative hearings.

Mr. DURRIN. I might add that for all of the drugs placed on schedule II, we have developed clear and convincing evidence of the high potential for abuse, and the severe dependence liability.

Mr. STURGES. Mr. Durrin, on page 5, you gave the number of propoxyphene-related deaths, reported by the consistently reporting of medical examiner panel, as 429 for 1976 and 528 for 1977, and you say these numbers come from a DAWN system computer tape. Yet these numbers are lower than the most recent quarterly report numbers: The quarterly report for April-June 1978, which is hot off the press, shows 480 deaths for 1976 and 599 for 1977.

What is the difference between the tape and the quarterly report?

Mr. DURRIN. Mr. Sturges, for the purpose of trending data, we go to our consistent panel of reports, which is 103, out of a total of 111 medical examiners in the systems from January 1975 through November 1978.

The reason for this is that we have had people drop in and out of the system, and, of course, this would skew the figures if we were to use that data for the purpose of trending the deaths.

What we have used in 1975, 1976, and 1977 is the consistently reported data, which of course is less than the total number of DAWN deaths. The higher figures are correct and accurate figures in terms of total number of deaths reported, but they are not comparable from year to year, because they would skew the data.

Mr. STURGES. Well, I thought these were the total consistent DAWN system numbers, but you are saying the latest quarterly report includes more than that?

Mr. DURRIN. They include the consistently reporting medical examiners, but they include several other medical examiners as well.

Mr. STURGES. As for data lag, virtually all of the numbers for the quarters involved are higher in the April to June report than they were in the January to March report, which goes to the point that information continues to roll in for 6 months, and even up to 2 years, after the reporting period.

Mr. DURRIN. That is correct, the numbers continue to increase, and we update as I said on a monthly basis.

You can draw no conclusion whatsoever from the 1978 figures at this point.

As I said, the first 3 months of 1978 are probably pretty much entirely in, indicating the deaths are continuing at about the same level as previously.

Senator LEVIN. The clear and convincing evidence test you have referred to is that what the law provides, or is that by regulation?

Mr. MILLER. Our regulations and the Administrative Procedures Act requires only substantive evidence, as distinguished from beyond a reasonable doubt, or by preponderance.

We only have to show there is substantial evidence, which is a whole lot less difficult to prove.

However, when we go into an administrative hearing, in making a determination as to whether propoxyphene should be moved from schedule IV to schedule II, we are in a full-fledged rulemaking area, and the data that is going to be submitted will have to be weighed through with witnesses, and statistics, and whatever information we may have, and, finally, it comes down to is there a substantial amount of evidence that the drug has a high potential for abuse; and secondly, does it have a severe dependence-producing liability.

That will be exceedingly difficult to do in an administrative area, because it will take a long time to do, and I can tell you that in case you do not know it, it took us nearly 7 years to control the tranquilizers.

We were tied up in hearings that never ended; we went through the court procedures and the difficulty in doing this administratively. If you have a drug that is very difficult to fit within the criteria within the Controlled Substances Act, and Congress sees that there is a need to control it quickly, and not take months and years, then the Congress will have to act. I can assure you, it will not be a simple case of the Government acquiring sufficient data that will constitute a certainty or substantial evidence that propoxyphene has a high potential for abuse, as distinguished from one that has a low potential for abuse. Meeting the criteria for schedule III and schedule IV as to whether or not it has a severe dependence-producing liability is not clear because all those schedules say dependence-producing liability relative to the higher schedule. Then drop down a schedule, and it says as less than that scheduled above, and you get down to another schedule, and you say dependence-producing liability relative to the other schedule, so the criteria are uncertain. All I am saying is that unless we get a great deal more information, that convinces us we can safely go into a hearing, it will take a long, long time to control it.

Senator NELSON. Thank you very much for taking the time to come to testify.

The committee will recess until tomorrow morning at 10.

[Whereupon, the committee was in recess until 10 a.m.]

[The prepared statement and supplemental information of Mr. Durrin follow:]

STATEMENT

of

MR. KENNETH A. DURRIN, DIRECTOR

OFFICE OF COMPLIANCE AND REGULATORY AFFAIRS
DRUG ENFORCEMENT ADMINISTRATION

U.S. DEPARTMENT OF JUSTICE

before the

Monopoly and Anticompetitive Activities Subcommittee

Select Committee on Small Business

United States Senate

Gaylord Nelson, Chairman

January 31, 1979

Dextropropoxyphene
(Darvon)

Chairman Nelson, Members of the Monopoly and Anticompetitive Activities Subcommittee: Gentlemen, I am very pleased to be here this morning representing the Drug Enforcement Administration at this hearing on the use and abuse of dextropropoxyphene.

Dextropropoxyphene, more commonly called propoxyphene, is related chemically and pharmacologically to methadone. Propoxyphene is used orally for the relief of mild to moderate pain.

Propoxyphene was first marketed in the United States in 1957 by the Eli Lilly Company under the trade name, Darvon. Within a few years, it became the most prescribed drug in America; twenty-two years later, it continues to maintain a considerable share of the market. In 1978, of the 1.4 billion prescriptions dispensed in retail pharmacies, 31.2 million were for products which contained propoxyphene. In this country, 59 companies now market approximately 150 products which contain propoxyphene alone or in combination with other substances. Almost half of these drugs are trade-name products. Clearly then, Mr. Chairman, any decisions regarding propoxyphene will have considerable impact on the pharmaceutical industry.

Propoxyphene is an abused drug and its abuse can and does lead to physical dependence. Propoxyphene is most often ingested. Intraveneous abuse of propoxyphene is usually a self-limiting process because of the resulting vascular and tissue damage. Patients who have histories of chronic pain, psychiatric disturbance, or multiple drug ingestion and who escalate the dosage of propoxyphene over rather long periods of time, abuse and/or become dependent on this drug. Patterns of abuse range from a single episode of ingestion to chronic daily use of high doses over long periods of time.

In 1976, when the Department of Health, Education and Welfare (HEW) concurred in the DEA proposal that propoxyphene be placed into Schedule IV of the Controlled Substances Act, the Secretary noted the following about the abuse potential and addiction liability of propoxyphene:

> The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less....Propoxyphene can produce a psychological and physical dependence which is qualitatively similar to that produced by 'classical' opiates (e.g., morphine or codeine) but which is quantitatively less.

Put another way, this means that propoxyphene affects most of the same systems of the body as morphine or codeine but the results are less intense.

Although it is seldom publicized, an important responsibility of the Drug Enforcement Administration is regulating the distribution of legitimate drugs and substances handled by legal drug importers, manufacturers and pharmacies, and prescribed by doctors. In conjunction with this aspect of our mission, DEA needs to be able to identify and evaluate the scope and extent of drug abuse in the United States. The Drug Abuse Warning Network--DAWN--has proven to be one of the major indicators in this area.

DAWN is a program that collects and analyzes data from hospital emergency rooms (DAWN ER's) and medical examiners (DAWN ME's) nationwide on a monthly basis in order to:

1. Identify drugs currently abused.
2. Determine existing patterns of abuse in a selected sample of Standard Metropolitan Statistical Areas (SMSA).
3. Monitor systemwide abuse trends including the detection of new abuse entities and new polydrug combinations.
4. Provide current data for the assessment of the relative hazards to health, both physiological and psychological for drug substances.
5. Provide data needed for rational control and scheduling of drugs of abuse.

To provide a standard from which all DAWN data is interpreted, DAWN statistics are reported in terms of specific drug abuse "mentions" involved in a hospital emergency room or drug-related deaths. Since DAWN accepts from one to six substances per episode, the drug mentions are equal to or exceed the number of episodes.

The ratio of propoxyphene emergency room mentions relative to all drug mentions in DAWN has remained essentially constant over the past three years, ranging from 2.4 percent in 1975 to 2.2 percent of all drug mentions in 1978.

In terms of frequency of being noted in emergency room reports, propoxyphene ranked seventh in 1975, 1976 and 1977. The next year, 1978, propoxyphene ranked eighth because phencyclidine came into more prominence. The substances mentioned more often than propoxyphene in DAWN emergency room reports are: diazepam (e.g., valium), alcohol (in combination with other drugs), heroin, aspirin, amitriptyline formulations (non-scheduled antidepressants), and flurazepam (a Schedule IV hypnotic related to diazepam).

Propoxyphene ranks third behind heroin and alcohol (in combination with other drugs) in terms of drugs associated with deaths in DAWN ME reports. Based on information received since January 1975 from medical examiners who have consistently reported to DAWN, the number of propoxyphene-related deaths is as follows:

1975	502
1976	429
1977	528*

Thus far, for 1978, 315 propoxyphene-related deaths have been reported by the above-mentioned panel of medical examiners. (Because there is considerable variation in the time which elapses between the date of death and the filing of the report, it will be six to nine months before statistically useful 1978 data is available.) Based on the 1975 through 1977 data, no consistent increase or decrease in the number of deaths is evident.**

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* All DAWN data was extracted from the DAWN system computer tapes identified as the "November 1978 System Tape". Comparisons across time are based on data received from the medical examiners who report to DAWN throughout the time period being studied. Collectively, these are referred to as a consistently reporting panel. Between January 1975 and November 1978, 1774 propoxyphene-related deaths were reported to DAWN from such a panel. Medical examiners who reported to DAWN but not throughout the entire period reported an additional 190 propoxyphene-related deaths. At various times, data from either panel has been released to the general public. As a result, there may be variations in the absolute numbers for the same time period.

** See pages 15 - 18 for the complete monthly data.

Throughout almost four years of availabld data, certain facets of propoxyphene abuse remain relatively constant. According to DAWN ER mentions for propoxyphene, over half of the time, 56 percent, suicide is the motivation behind the incident. Psychic effect accounts for 13 percent; dependence accounts for another 5 percent of the reasons for propoxyphene abuse. In the remaining 26 percent of the cases, DAWN does not record a specific motivation.

According to DAWN ME mentions, the following were recorded as the manner of death:

suicide	44%
accidental (unintentional overdose) - motivation for taking drug unknown	22%
accidental (unintentional overdose) - motivation for taking drug psychic effect or dependence	13%
undetermined	21%

I cannot present to you a profile of a propoxyphene abuser, because there is no clear-cut demographic model. There are a greater number of propoxyphene-related mentions in the 20-29 age range, accounting for 40 percent of all ER mentions and 35 percent of all ME mentions. Women tend to be involved in propoxyphene-related incidents more often than men, representing 59 percent of all ER mentions and 53 percent of all ME mentions. In proportion to their respective

population size nationally, blacks are reported less frequently than are whites. It is noted that, for both ER episodes and ME mentions, white females over age 50 have a disproportionate number of mentions.*

Where do these individuals obtain propoxyphene? Based on DAWN ER data, legitimate prescriptions are used at least 58 percent of the time. This contrasts sharply with the one (1) percent reported as obtained through a street buy or the four (4) percent obtained via other illegal activity such as theft and forged prescriptions. No source is recorded for approximately a third, 37 percent, of all incidents. There is no known clandestine manufacture of propoxyphene.

Prior to comparing the DAWN data regarding propoxyphene to other controlled substances, I believe it is important to digress for a moment to discuss scheduling -- that mechanism by which controlled substances are classified into one of five categories or schedules.

Procedures for the control of dangerous drugs were established under the Controlled Substances Act of 1970 (CSA). It is very important to bear in mind that drug scheduling actions are not solely the responsibility of the DEA; we work very closely with HEW, and at the Staff level with the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA).

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* See pages 19 and 20 for complete data.

Simply stated, drugs are scheduled according to their abuse potential and currently accepted medical use, somewhat in the following manner:

Schedule I : No accepted medical use in the United States; high abuse potential

Schedule II : Currently accepted medical use; high abuse potential with severe psychic or physical dependence liability

Schedule III: Abuse potential less than those in Schedules I and II

Schedule IV : Abuse potential less than Schedule III

Schedule V : Abuse potential less than Schedule IV

The regulatory requirements are established based on these same schedules. Regulatory requirements include, but are not limited to, aspects of registration, recordkeeping, distribution restrictions, dispensing limits and manufacturing quotas.

There was an ongoing debate between 1956, when the issue of control was first raised, and 1977, when propoxyphene was placed into Schedule IV of the CSA, regarding whether this drug posed a public health hazard, the kind and magnitude of which warranted greater controls on its manufacture and distribution. In these debates, the issue of severity of abuse potential and addiction liability of propoxyphene compared to morphine-like drugs was always paramount. The 1957 findings of Drs. Fraser and Isbell

of the Public Health Service Addiction Research Center that, "...(propoxyphene's) overall addiction liability is estimated to be no greater, and is probably less, than that of codeine" were repeatedly confirmed.

In 1973, DEA first proposed to HEW that propoxyphene be placed under control. HEW did not feel control was warranted at that time, but that we should continue to monitor the drug. In March 1976, DEA submitted updated information to HEW regarding the abuse of propoxyphene. The ensuing deliberations resulted in HEW's recommendation to control propoxyphene in Schedule IV, and DEA controlled the drug effective March 14, 1977. Thus, unauthorized manufacture, distribution and possession of propoxyphene became a criminal offense. Labeling carries a CIV symbol, annual inventories by manufacturers and distributors are required and prescriptions may be refilled no more than five times and are valid from date of issuance for only six months.

The scheduling of propoxyphene is once again controversial. There are proponents who now maintain that propoxyphene more correctly belongs in Schedule II. The Public Citizens Health Research Group and the Oregon Department of Human Resources have petitioned to place propoxyphene in Schedule II. In response to these petitions, DEA has undertaken a survey to update information on the abuse of propoxyphene. Data regarding the nature and extent of propoxyphene-related unlawful or unprofessional activities has been solicited from each State government. Data is being assembled from several other sources: DAWN, DEA lab analysis of

evidentiary exhibits, DEA enforcement case files, compliance investigations, theft reports and the scientific and medical literature. I anticipate that this information will be assembled and evaluated by early Spring of this year. Shortly thereafter, these findings will be submitted to HEW for its evaluation of the medical and scientific issues associated with the petition for rescheduling.

Since criteria for scheduling is largely based on potential for abuse and the severity of psychological or physiological dependence, I think that it may be valuable to use the available abuse data to compare propoxyphene with other drugs in Schedules II and IV.

In terms of the DAWN ME mentions per million prescriptions dispensed in retail pharmacies, propoxyphene falls in the same general class as codeine (Schedule II, III), meprobamate (Schedule IV), diazepam (Schedule IV) and Amitriptyline formulations (unscheduled).

The Schedule II drugs responsible for a substantial portion of the DAWN ME mentions, are implicated in deaths at least ten times more frequently than propoxyphene. For example:

pentobarbital	178	mentions per million Rx
seco/amobarbital	234	" " " "
secobarbital	259	" " " "
Amobarbital	416	" " " "*

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* See page 21 for the complete list.

These figures are contrasted with propoxyphene which is implicated in 15 deaths per million prescriptions dispensed.

Propoxyphene mentions from DAWN hospital emergency rooms show that approximately 115 ER mentions occur per million prescriptions dispensed. By comparison, for diazepam, another Schedule IV drug and the drug most often involved in DAWN ER reports, there are 386 mentions per million prescriptions dispensed.

A significant question, and one that has a great bearing on the outcome of the pending petitions, is "Has placing propoxyphene in Schedule IV as of March 1977 had an impact on its abuse?" With respect to DAWN ER mentions, I can point to a statistically significant decrease since that time.*

At the present time, there is insufficient data with respect to DAWN ME reports to allow one to make a comparable claim. It will be another six to nine months before the 1978 data is completed.

Also worth noting is the diversion problem, or more precisely, the lack of one. While there has been some diversion of propoxyphene through thefts from registrants, it does not appear to be a preferred drug by thieves. This

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* See pages 17 and 18 for specific data.

is in sharp contrast to the well-orchestrated attempts to divert such drugs as the amphetamines, phenmetrazine (preludin), the barbiturates, methaqualone, methadone, and hydromorphone (Dilaudid) -- all Schedule II substances. Similarly, fraudulent prescriptions and illegal dispensing are not problems with propoxyphene as they are with the other drugs I just noted.

Nevertheless, the DEA is most concerned about the abuse of propoxyphene; the sizable number of deaths alone is cause for constant monitoring and interest in this problem. The toxicity problem is very real.

Consideration should be given to several possible options in order to determine the best means of addressing the toxicity problem. The petitions set forth two of these: removal of propoxyphene from the market or placement in Schedule II. The questions of medical usefulness of propoxyphene and the need for its continued marketing are determinations for HEW and the FDA, and DEA does not presume to venture into that area.

As to rescheduling, under the provisions of the CSA, DEA has moved into Schedule II substances that we believe had a high popularity among abusers and which are available on the streets in significant quantities. For example, we rescheduled amphetamines, fast-acting barbiturates,

phencyclidine and methaqualone. We will be looking for data of a similar nature in the study on propoxyphene now underway to determine whether it meets Schedule II criteria. In addition, HEW's recommendation is required as part of the scheduling process.

The majority of DAWN ER propoxyphene mentions center around legitimate prescriptions. While Schedule II prescriptions are not refillable, an average propoxyphene prescription is 40 dosage units and the experts tell us it takes approximately 20 dosage units to cause death--probably less in combination with alcohol or other drugs.

If HEW (FDA) determines that removal from the market is not appropriate, it seems to us that there are additional options within FDA's purview over drug usage which directly address the toxicity problem. These include:

-- A labeling change, perhaps a boxed warning, which would strengthen the warning to physicians of the toxicity problem and of the use of the drug in suicides.

-- A curtailment of the indications for use which would limit the drug's use to those conditions where it is clearly superior to other less toxic substances.

-- Discouragement of use, again through a labeling change, for the chronic, long-term conditions which would necessitate that the patient continually have sizeable quantities of the drug on hand.

-- A patient package insert which would warn the patient of the drug's dangers.

Only the Food and Drug Administration can pass upon the viability of these suggestions. Certainly, a review of propoxyphene's potency, efficacy and risk-benefit ratio by FDA's medical experts is in order in light of the questions raised in the petition by Dr. Wolfe and the Public Citizen Health Research Group. In support of this, the Drug Enforcement Administration will provide appropriate data to the FDA.

Whatever the mechanism, it is imperative that every effort be made to substantially reduce the number of propoxyphene-related deaths. The Drug Enforcement Administration will work to this end.

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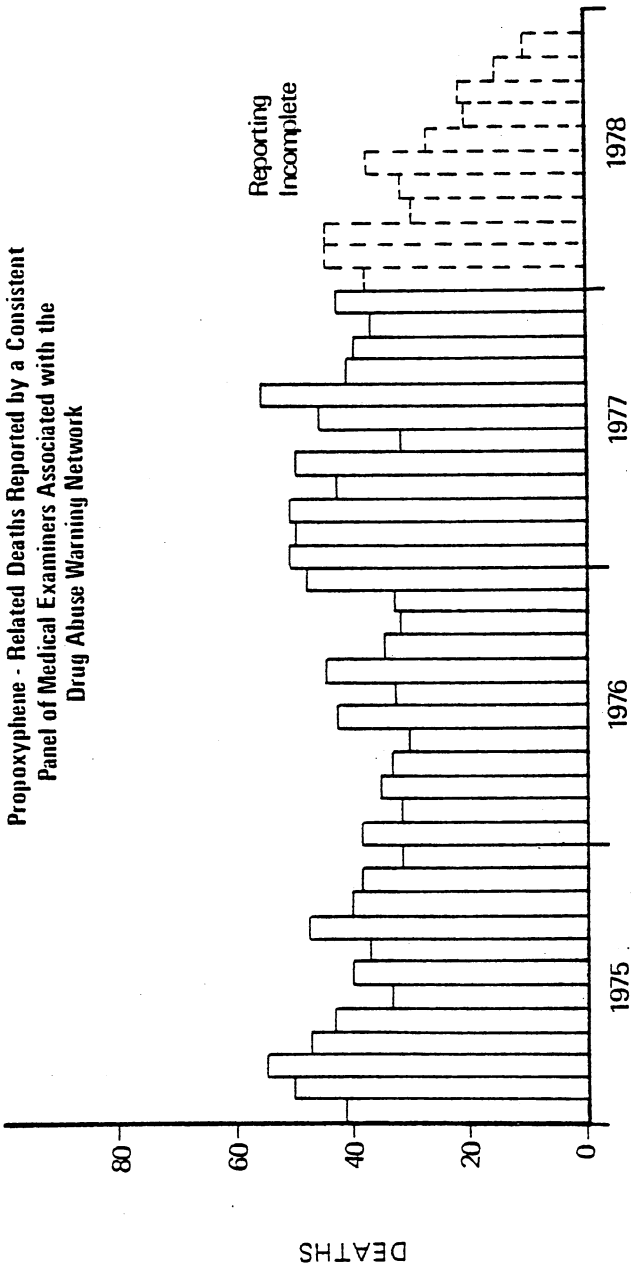


Source: DEA DAWN Computer Tape Through November 30, 1978
Printout: January 16, 1979. pgs. 21–24 Captioned: D - Propoxyphene vs. All Other Drug/Substances

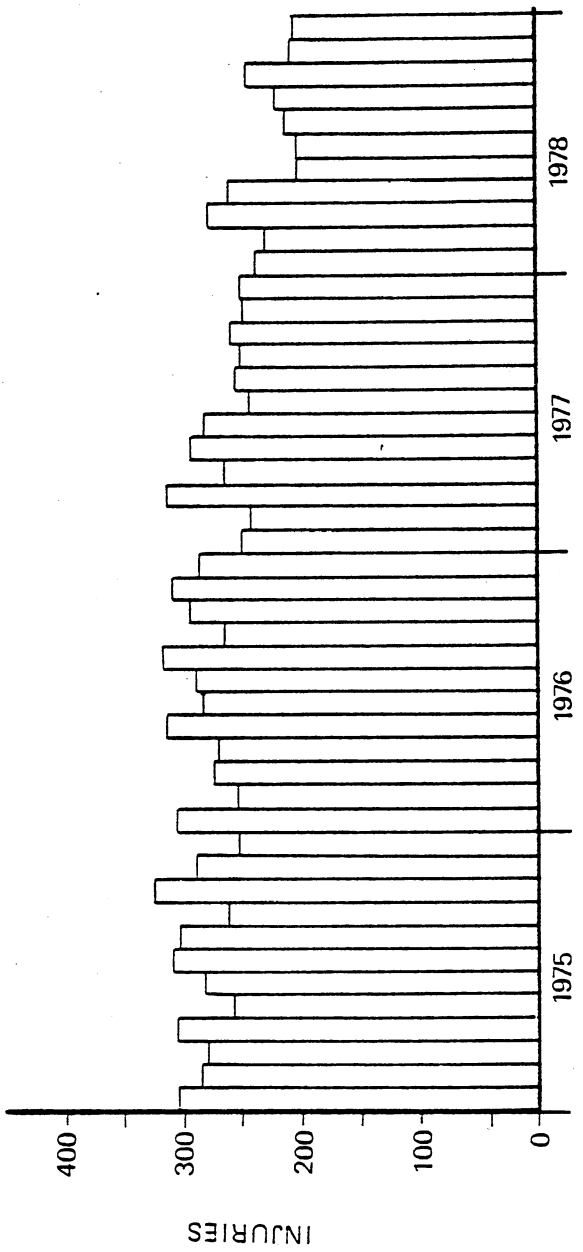
Propoxyphene Related Deaths Reported by a Consistent Panel of Medical Examiners Associated with the Drug Abuse Warning Network

	1975	1976	1977	1978*
January	41	38	50	37
February	50	31	49	44
March	55	35	50	44
April	47	33	42	29
May	43	30	49	31
June	33	42	31	37
July	40	32	45	27
August	37	44	55	20
September	47	34	40	21
October	40	31	39	15
November	38	32	36	10
December	31	47	42	

* Deaths occurring within the last 6 to 9 months are under-reported due to the reporting procedures used by the Medical Examiners.

Sources: DEA DAWN November 1978 System Tape Printout: January 16, 1979, pg. 21-24, captioned D-propoxyphene vs. all other drugs/substances.

Propoxyphene - Related Injuries Reported by a Consistent Panel of Emergency Rooms Associated with the Drug Abuse Warning Network



Source: DEA DAWN Computer Tape Through November 30, 1978
Printout: January 16, 1979, pgs. 17–20 Captioned: D - Propoxyphene vs. All Other Drug/Substances

Propoxyphene-Related Injuries Reported by a Consistent Panel of Emergency Rooms Associated with the Drug Abuse Warning Network

	1975	1976	1977	1978
January	306	305	250	239
February	286	254	243	230
March	281	274	315	278
April	306	270	266	261
May	259	316	294	202
June	283	285	282	198
July	309	289	245	212
August	303	319	256	219
September	262	269	251	247
October	327	295	259	210
November	289	310	249	206
December	253	288	251	

Source: DEA DAWN November 1978 System Tape Printout: January 16, 1979, pg. 17-20, captioned D-propoxyphene vs. all other drugs/substances.

A standard nonparametric test procedure known as the Mann-Whitney U test was used to test the levels of propoxyphene mentions for significant differences between the time periods before and after CSA controls (March 14, 1977) were instituted, i.e., January 1975 - February 1977, and April 1977 - November 1978, respectively. This test was chosen for its generality and particularly for its freedom from the normality assumptions required for most comparable test procedures. According to the results of this test at the 95% confidence level, the number of propoxyphene mentions reported by consistently reporting DAWN emergency rooms was significantly lower during the time period following the institution of CSA controls.

Reference for Mann-Whitney U test: Nonparametric and Shortcut Statistics in Social, Biological, and Medical Sciences by Merle W. Tate and Richard C. Clelland, pages 89-91 and 137; published by Interstate Printers and Publishers, Inc., Danville, Illinois (1959).

Age, Race and Sex of Propoxyphene Users Based on
DAWN Emergency Room Mentions: January 1, 1975, to November 30, 1978

Race-Sex \ Age	1 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50+	Unknown	Total N	Total %
White Male	5	633	1,389	596	292	227	19	3,161	
Black Male	2	143	389	156	49	32	8	779	
TOTAL MALE	7	776	1,778	752	341	259	27	3,940	(24.5)
White Female	1	1,631	2,619	1,400	803	559	53	7,066	
Black Female	0	709	1,092	419	173	78	24	2,495	
TOTAL FEMALE	1	2,340	3,711	1,819	976	637	77	9,561	(59.3)
Other Race - Both Sexes + Unknowns	2	692	1,005	511	227	139	36	2,612	(16.2)
TOTAL N	10	3,808	6,494	3,082	1,554	1,035	140	16,113	
TOTAL %	(0.1)	(23.6)	(40.3)	(19.1)	(9.6)	(6.4)	(0.9)		(100)

Source: DEA DAWN November 1978 System Tape Printout: January 9, 1979, pg. 1-14, Captioned Race and Sex Groupings.

Age, Race and Sex of Propoxyphene Users Based on
DAWN Medical Examiner Mentions: January 1, 1975, to November 30, 1978

Race-Sex \ Age	1 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50+	Unknown	Total N	Total %
White Male	0	52	327	173	77	83	0	712	
Black Male	0	13	73	35	12	1	0	134	
TOTAL MALE	0	65	400	208	89	84	0	846	(43.1)
White Female	0	48	194	175	203	239	3	862	
Black Female	0	33	73	40	26	9	0	181	
TOTAL FEMALE	0	81	267	215	229	248	3	1,043	(53.1)
Other Race - Both Sexes + Unknowns	0	9	28	23	8	7	0	75	(3.8)
Total N	0	155	695	446	326	339	3	1,964	
Total %	(0.0)	(7.8)	(35.4)	(22.7)	(16.6)	(17.3)	(0.2)		(100)

Source: DEA DAWN November 1978 System Tape Printout: January 9, 1979, pg. 16-26, Captioned Race and Sex Groupings.

Drug-Related Deaths in Relation to Availability of Drugs*

	1975-1977 DAWN ME Mentions	Mentions/ Million Prescriptions**	CSA Schedule
Heroin	4618	N.A.	I
Alcohol plus other drugs	4059	N.A.	0
Propoxyphene	1642	15	IV
Diazepam	1300	8	IV
Methadone	1296	N.A.	II
Secobarbital	1229	259	II
Amitriptyline formulations	958	18	0
Pentobarbital	947	178	II
Seco/Amobarbital	821	234	II
Phenobarbital	815	31	IV
Codeine	621	5	II,III
Aspirin	530	N.A.	0
Amobarbital	451	416	II
Ethchlorvynol	441	75	IV
Glutethimide	318	47	III
Meprobamate	274	10	IV

* Drugs which accounted for 74% of DAWN Medical Examiner mentions.

** Mentions were collected from Standard Metropolitan Statistical Areas which include approximately a third of the population. Prescription data was collected nationwide. The number of deaths per million prescriptions would be proportionately higher for each drug if nationwide death statistics were available.

Source ME Mentions: DEA DAWN November 1978 System Tape Printout: January 9, 1979, pg. 6-10, captioned Totals For Grouped Years.

KENNETH A. DURRIN

Since October 1976, Mr. Durrin has been the Director of the Drug Enforcement Administration Office of Compliance and Regulatory Affairs. From 1969 to that time, he was in charge of the Compliance Programs for DEA and its predecessor agencies. Mr. Durrin has been a career Federal Investigator since his graduation from Albany Law School, Union University, in 1952. He is a member of both the American Society for Industrial Security and the International Association for Chiefs of Police.

FACT Sheet

United States Department of Justice
Drug Enforcement Administration

Compliance and Regulatory Affairs

DEA's mission is not only to stop the flow of illicit drugs in this country, but also to regulate the distribution of legitimate drugs--substances handled by the legal drug importers, manufacturers and pharmacies, and prescribed by doctors.

Along these lines DEA has the responsibility for monitoring the importation of legitimate drugs into the United States and reviewing all import-export activities in line with existing treaty obligations.

Abuse of these legitimate drugs is substantial. According to a nationwide study of the National Institute on Drug Abuse (NIDA), "... the non-medical use of psychotherapeutic drugs ranks second to marihuana among youth and all adults ...," with "one in ten young people and one in seven adults having some non-medical experience with an over-the-counter or prescription sedative, tranquilizer or stimulant."

DEA's experience has been that when an addict is unable to find his illicit drug of choice--for example heroin or cocaine--he will tend to substitute the legitimate drugs. During a heroin shortage, for instance, we are increasingly likely to uncover forged prescriptions, non-medical drug purchases, drug burglaries and employee drug theft--in other words, diversion of licit drugs for illicit purposes.

DEA's regulatory program--established to minimize this diversion--pursues an essential, although seldom publicized, DEA mission.

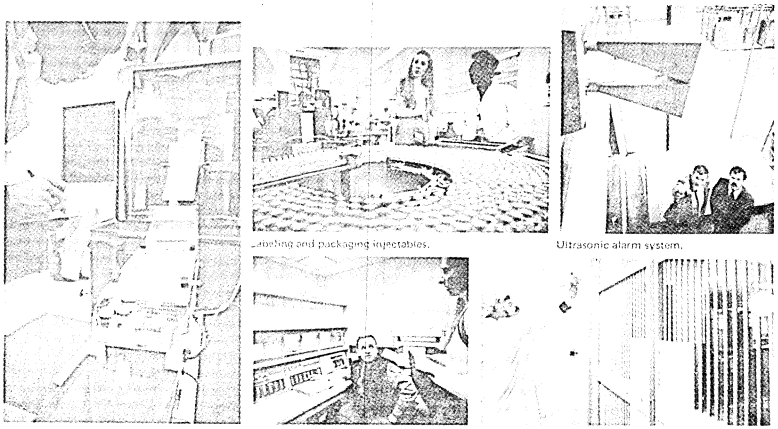
In October 1976, in recognition of the importance of DEA's regulatory mission and in order to consolidate regulatory functions, the Office of Compliance and Regulatory Affairs was formed. This is a principal office and reports directly to the Administrator and Deputy Administrator. The new Office brings together registration, regulatory control and investigative activities formerly the responsibility of the Compliance Investigations Division in DEA's Office of Enforcement, and the drug scheduling and drug information activities formerly the responsibility of the Special Programs Division of the Office of Science and Technology. Dialogue with the pharmaceutical industry and the Department of Health, Education and Welfare shows that this action should be a step forward in raising the level of importance of Compliance and Regulatory Affairs within our own agency and improving DEA'S effectiveness with other agencies and the pharmaceutical industry.

The regulatory mechanism as created by the Controlled Substances Act (CSA) of 1970 centers upon a "closed distribution system," the cornerstone of which is the required annual registration of all handlers and prescribers of controlled substances. DEA now has more than 570,000 registrants and collect more than $2.7 million in annual registration fees.

Controls begin with a pre-registration investigation of all wholesale handlers. This preliminary step is taken to ensure that registration is in the public interest (that is, that the firm has adequate security, no violative history, State approval, etc.). It also ensures that those within the firms who are responsible are knowledgeable of requirements under the Controlled Substances Act.

Following registration, under this program DEA monitors and periodically investigates registrants to ensure they are accountable for the controlled substances handled. When violations are uncovered, appropriate action is taken.

Since the passage of the Controlled



Tablet compression machine making methadone. Computerized security control center. Raw materials vault/alarm system.

The above photographs were taken at Eli Lilly and Company, Indianapolis, during a DEA Compliance visitation.

Substances Act which took effect in May 1971, DEA has accomplished a number of important actions, not the least of which relates to drug scheduling action. These actions, of course, are not our exclusive mandate; in making our recommendations we work very closely with the Food and Drug Administration and the National Institute on Drug Abuse. Examples of these actions would be the moving of Phencyclidine (PCP) from Schedule III to Schedule II and the March 14, 1977 final order placing dextropropoxyphene (Darvon, et al.) under control in Schedule IV. Since May 1971, we have controlled 35 drugs, have moved eleven drugs to another schedule and have decontrolled six drugs. In addition, controls on several hundred commercial preparations which contain controlled substances have been lessened by classifying these products as exempted, excepted or excluded.

Simultaneous to rescheduling certain drugs we also establish production quotas for those substances. Quotas create smaller inventories and a less zealous marketing atmosphere which, when coupled with stringent security and regulatory safeguards on prescribing and dispensing the drugs, substantially reduce the potential for diversion. In setting quotas, DEA again relies heavily upon the FDA to furnish with estimates of legitimate medical need.

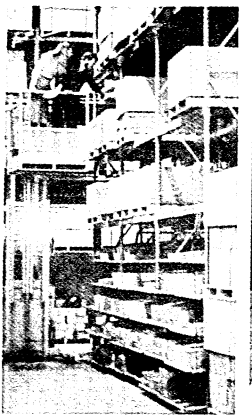
For example, just prior to Schedule II control, in 1971, U.S. amphetamine production was approximately 66,000 pounds per year. The quota for 1977 is 7,700 pounds.

Despite this cutback --- drastic though it may seem --- no one with a legitimate need for these drugs has been deprived. As with amphetamines, substantial production decreases have also been effected on phenmetrazine (Preludin), methaqualone (Quaalude, et al.) and the three fast-acting barbiturates, amobarbital, secobarbital, and pentobarbital.

While success has been obtained in reducing diversion at the manufacturer/distributor level, success at the retail level (e.g., physicians, pharmacies) is much less dramatic. Under the Controlled Substances Act, the primary responsibility at this level is left with the States. DEA is required to register every professional who possesses a valid State license, unless he has a drug felony conviction or materially falsifies his registration application.

However, the number of retail registrants totals more than 50,000, and State police are

' thick distribution vault for Schedule II substances.



Inside the distribution vault.

An audit of accountability.

limited in the resources they can devote to handling this number.

In keeping with DEA's legislative mandate, DEA is devoting all possible attention and resources to this problem. Memoranda of Understanding have been signed with 45 States and the District of Columbia delineating Federal/State roles. We have also developed a State criminal investigative operation targeted against willful retail registrant diversion. This operation, called the Diversion Investigative Unit (DIU) program is DEA supported, State run and State manned.

Another example of DEA's Federal/State cooperative effort involves the assistance afforded by DEA in the development and implementation of individual State Mini-DAWN Networks.

Additionally, a Voluntary Compliance Program has been established. This program has direct responsibility for coordinating DEA's efforts to obtain self-regulation from State regulatory agencies, health professionals and their respective associations. This program is aimed at increasing registrants' efforts to prevent diversion and to direct their interest in upgrading their level of self-regulation and self-enforcement.

The Office of Compliance and Regulatory Affairs also maintains the following three unique computerized systems:

1. Drug Abuse Warning Network (DAWN)

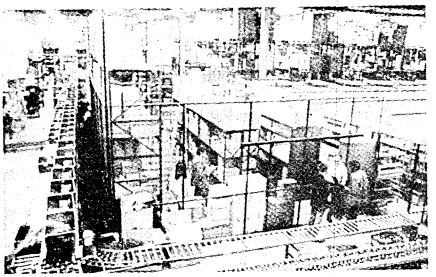
Project DAWN (Drug Abuse Warning Network) is a federal program initiated by the Drug Enforcement Administration to assist the government in identifying and evaluating the scope and extent of drug abuse in the United States. DAWN, jointly funded by the National Institute on Drug Abuse (NIDA) includes over 900 different facilities which supply data to the program. The original design and development of the program was conceived by the scientific staff of the Office of Science and Technology in the Drug Enforcement Administration. The system is used as a means to assist the officials and others concerned with the problems of drug abuse to identify the parameters of the drug abuse phenomenon. DAWN represents a continuing and dynamic effort that will be constantly reviewed and modified to obtain more precise information upon which regulatory decisions can be based.

2. Automated Reports and Consolidated Order System (ARCOS)

ARCOS is a computerized system which provides for the monitoring of drug transactions of selected controlled substances. These transactions are reported by approximately 2,000 manufacturers, distributors, importers and exporters. The system provides a government capability to monitor the selected controlled substances from point of import or manufacture to point of export or distribution to the dispensing level. The system processed approximately 17.5 million transactions in FY77, an increase of 3.6 million over FY76.

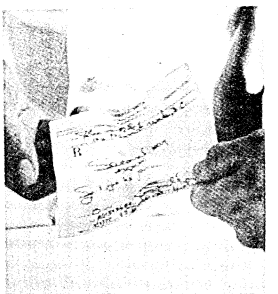
3. Project Label

This program represents a systematic and computerized activity of continuously updating and maintaining a listing of all products containing controlled substances currently marketed by trade and generic name, by manufacturer, by components and composition, by acquisition and NDC number and by appropriate CSA Schedule.



A major drug wholesaler's caged area for storage of Schedule III, IV, and V drugs.

Compliance Investigator observing the procedures for filling an order for a Schedule III, IV, or V drug, at Henry Gilpin Company, Washington, D.C.



Control of prescriptions is a key to drug control.

FACT Sheet

United States Department of Justice
Drug Enforcement Administration

The Diversion Investigation Unit Program

Office of Compliance and Regulatory Affairs

The term "illicit drug traffic" is actually a generalization covering a number of types of drugs and their movement to various groups of abusers. For example, the traffic in heroin from Southeast Asia is distinct from the traffic in cocaine from Latin America. Similarly, the traffic in LSD from clandestine laboratories differs from the traffic in diverted legitimate drugs.

In a broad sense, the illicit drug traffic can be viewed as consisting of three facets:

(a) Traffic originating in foreign countries
(b) Traffic originating in domestic clandestine laboratories
(c) Traffic originating through diversion from legitimate commerce.

Traditionally, Federal, State and local governments have given overwhelming priority to combating the traffic originating in foreign countries (e.g., heroin, cocaine, marihuana). To a lesser extent, efforts have been expended on combating the traffic originating in domestic clandestine laboratories (e.g., LSD). The lowest priority had been given to combating diversion from legitimate commerce (e.g., amphetamines, barbiturates, tranquilizers, etc.).

There was a reason for this. In deploying the limited resources of law enforcement, heavy consideration must be given to the relative harm to society caused by these various drugs. If the harm caused by drug A is greater than that caused by drug B (whether due to the amount of abuse or the innate characteristics of the drug), then emphasis must be placed on combating the traffic in drug A. Traditionally, the illicit drugs originating from foreign sources have been viewed by law enforcement and the public as the most harmful.

In recent years, however, we have witnessed a shift in the market towards what has been termed "poly-drug" abuse. Without delving into a statistical or sociological analysis of this trend, suffice it to say that the legally produced drugs used in treating various illnesses in this country are becoming more prevalent in the illicit market. As the demand increases, so follows the supply.

We do not believe this shift in the market is such as to require a dramatic shift of law enforcement priorities and resources. We do believe, however, that a limited shift is necessary. Furthermore, this shift will have to take place primarily at the State and local levels of law enforcement.

The working legislation of DEA is the Controlled Substances Act of 1970. A study of this Act will show that DEA has been given considerable authority to monitor the commerce of controlled drugs at the manufacturing and wholesaling levels. Its authority at the retail level is markedly less.

The rationale of Congress in limiting Federal authority at this level was threefold: (1) to conduct the same degree of scrutiny at this level as at the other levels would require a very large increase in Federal resources; (2) the responsibility for monitoring this level has traditionally been held by the States; and (3) the business sphere of the manufacturers and wholesalers is of an interstate nature, while the business sphere of the retail handlers is of intrastate nature.

Due to resource and legal restraints then, there is a marked difference between the strong Federal presence at the upper levels of the drug industry and the inherently lesser Federal presence at the retail level.

There is little commonality in the nature and extent of regulation of health professionals by State governments. The most prevalent mode is to assign this responsibility to various

regulatory boards (i.e., Board of Pharmacy, Board of Medicine, etc.). These boards are generally responsible for the full regulation of professional practice within the State which encompasses a broad range of issues, only one of which is the prevention of diversion.

For example, a Board of Pharmacy may be responsible for monitoring continuing education requirements, coordinating reciprocity of licensure with other States, monitoring the professional ethics of pharmacists in the State, assuring that the pharmacies are properly equipped and staffed, and a number of other issues which, although vital to the practice of pharmacy, have little to do with combating the criminal diversion of drugs by pharmacists. Its staff, if there is one at all, may consist of one or two investigators for the entire State. This staff may even consist of practicing pharmacists who work for the Board on a part-time basis. This bleak picture of the Boards of Pharmacy becomes good by comparison with the boards of other professions. These other boards are so poorly equipped that in many States they rely upon the Board of Pharmacy's staff to conduct investigations of their professions.

The pattern among all these boards is that they are not oriented, equipped, staffed, trained, or in some instances even empowered, to properly combat diversion by the health professionals they are charged with regulating. These shortcomings are not the fault of the boards. In our experience, they are fully aware of their deficiencies, but are unable to alleviate their situation. The causes for this are complex, but essentially derive from a lack of public awareness of this facet of the illicit drug problem.

The State law enforcement agencies (State Police, State Bureau of Investigation, etc.)

DEA Compliance Investigator conducts an audit at Henry Gilpin Company, Washington, D.C.

do not oftenl pursue the diversion of drugs by health professionals in any real sense. The same can be said for local police departments within the State. This is primarily due to the traditional assignment of this responsibility to the regulatory boards. Other contributing factors include a lack of resources, and a lack of training and orientation in this area.

The State and local prosecutors as a general rule have no experience in prosecuting criminal cases against health professionals. There is even a reluctance to accept such cases due to their oddity, sensitivity, or complex nature. In sum, there is little Federal, State, or municipal effort expended on curtailing diversion of drugs from the retail level.

There are about 15 billion dosage units of controlled drugs manufactured in the United States each year. Based upon subjective and statistical indicators, the most conservative estimates on the extent of diversion of these

Control of prescriptions is a key to drug control.

Retail pharmacy work space.

drugs range between 200,000,000 and 250,000,000 dosage units per year. Some estimates greatly exceed this range.

Based upon surveys of cases and conservative projection, about 90 percent of this diversion is occurring at the retail level. This would be expected, since there is relatively little energy being expended to stop it.

Diversion at the retail level can occur in a number of ways; the most predominant of which are criminal diversion by a health professional (or an employee thereof), forged prescriptions, and theft. Among these, the most predominant is criminal diversion.

Eliminating criminal diversion at this level requires the availability of a broad range of techniques, authorities, and mechanisms. These include the following:

A thorough ability to conduct enforcement/regulatory operations within the drug industry, down through the practice of pharmacy and medicine. This should be suffrcient to identify and act upon regulatory and criminal violations by a health professional.

A thorough capability in law enforcement techniques, including surveillance, undercover techniques, rules of evidence, arrest and search procedures, court testimony, etc.

A full set of available sanctions ranging from administrative through regulatory to criminal prosecution, depending upon the nature of the violations and the situation.

The ability to use sanctions available at both the Federal and State levels.

Resources and support to conduct such operations on a scale sufficient to have an impact on the problem.

There is essentially no existing entity at the Federal, State, and local level with these capabilities.

To summarize the foregoing, the diversion of drugs from legitimate industry has been a lesser area of public and governmental attention. Due to shifting trends with the drug traffic, however, this facet of the drug problem is becoming more important. Law enforcement and regulatory agencies at all levels must begin making some adjustments to it.

The adjustment that a growing number of States are finding to be sufficient and meaningful is the Diversion Investigation Unit Program.

Under this program, DEA serves as a catalyst to bring funding, manpower, expertise and scattered jurisdiction together into a unified effort. These units are manned and run by State authorities. They are trained by DEA; and a DEA Agent is assigned on a full-

Investigators taking inventory inside vault for Schedule II drugs, with a representative from the Henry Gilpin Company, Washington, D.C.

time basis to supply continuing expertise and support.

The DIUs are designed to draw on the experience of a varied group of investigators; including those from State regulatory boards, State law enforcement agencies, and DEA. These investigators, when assigned to the DIU, are released from other duties in their respective agencies to enable them to concentrate solely on diversion cases.

To ensure that no single agency has complete control over the unit, a Policy Board is established. Each concerned agency has one voting member on the Policy Board. The Policy Board provides overall direction and support for the unit.

Training is an integral part of the DIU concept. The investigators assigned to the units receive a specialized training course, normally of one-week duration, in the procedures involved in developing criminal cases against violative registrants.

In order to obtain the necessary prosecutive follow-up, special seminars are held by DEA for district attorneys and county prosecutors to school them in the fine points of prosecuting diversion cases. Judges are also invited to attend these seminars.

The DIU was conceived as a "seed" program. Its objective was to launch the participating State off to a sound start by means of direct Federal funding and support, and ultimately to have a State-sustained, permanent, DIU-type program. The program was initiated on a pilot basis in Texas and Michigan in September 1972 and shortly thereafter in Alabama (December 1972). All three pilot States have endorsed the program and are still operating them under State funding.

Upon success of these pilot programs, plans were made to implement DIUs in seven additional States. These were: California, Illinois, Massachusetts, New Jersey, Pennsylvania, North Carolina and Florida. All but Florida are still in operation. New Units are now operating in Georgia, New Hampshire, Nevada, Washington, Hawaii, Main, and the District of Columbia. Three more states will join the program in FY-79.

The DIU Program has demonstrated how a concerted effort of highly trained personnel can curtail the diversion of drugs on a Statewide level. The project brings together those independent State agencies that have a role in regulatory drug enforcement into a single, cohesive unit. Each agency contributes specialized skills to the benefit of the other participants in the unit. State police assigned to the units have become expert in the area of regulatory investigations. Likewise, regulatory inspectors have become expert in the techniques of criminal investigation. In effect, a cross-fertilization of experience, training, and knowledge has taken place.

The DIU is an excellent example of what can be accomplished when concerned State agencies unite in a cooperative effort with Federal agencies to suppress the illicit diversion of controlled substances.

FACT Sheet

United States Department of Justice
Drug Enforcement Administration

DAWN
(Drug Abuse Warning Network)

Project DAWN (Drug Abuse Warning Network) is a federal program initiated by the Drug Enforcement Administration (DEA) to identify and evaluate the scope and extent of drug abuse in the United States. DAWN, jointly funded with the National Institute on Drug Abuse (NIDA) includes over 900 different facilities which supply data to the program. The original design and development of the program was conceived by the scientific staff of the Office of Science and Technology in the Drug Enforcement Administration. Since its inception in June 1972, the Project DAWN contract has been negotiated on six separate occasions. Each separate negotiation usually involved some modification in the areas of (1) SMSA coverage, (2) number and types of participating facilities, and (3) time collecting intervals associated with Project DAWN, I, II, III, IV, V, VI, and VIII. (See chart, DAWN Systems Statistics, below)

The Purposes of DAWN

DAWN has been designed to:

1. Identify drugs currently abused.
2. Determine existing patterns of abuse in a selected sample of SMSA's (Standard Metropolitan Statistical Areas).
3. Monitor systemwide abuse trends including the detection of new abuse entities and new polydrug combinations.
4. Provide current data for the assessment of the relative hazards to health, both physiological and psychological, and relative abuse potential for drug substances.
5. Provide data needed for rational control and scheduling of drugs of abuse.

DAWN SYSTEM STATISTICS

Correlation between designated DAWN-Phase citation and time interval of data collection period.

Designation	*Time Interval*
DAWN I	September 1972 - March 1973
DAWN II	April 1973 - March 1974
DAWN III	April 1974 - April 1975
DAWN IV	May 1975 - April 1976
DAWN V	May 1976 - April 1977
DAWN VI	May 1977 - April 1978
DAWN VII	May 1978 - April 1979

Information Collected

DAWN, which has been in existence since July 1972, and in essentially its current format since July 1973, derives its information from episode reports provided by selected hospital emergency rooms, medical examiners and crisis centers. A reporter in each participating facility completes a report for each drug abuse contact seen by the facility.

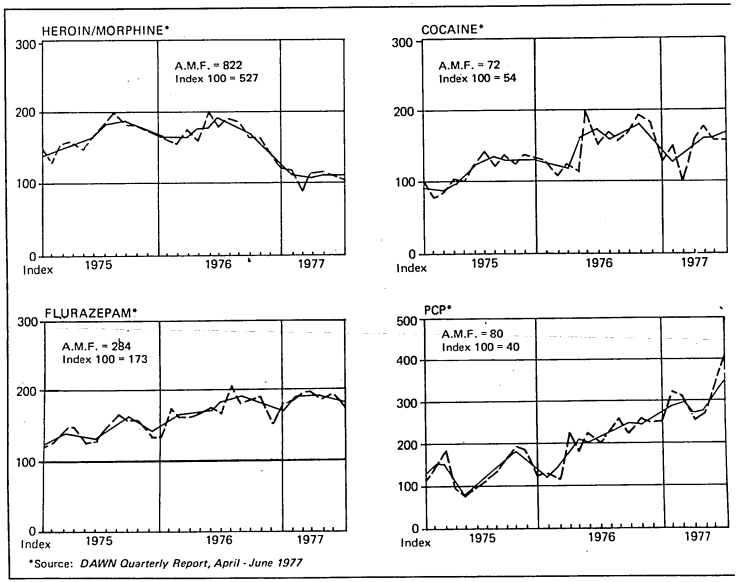
The reasons for contact are medical or psychological in nature (hospital emergency rooms and crisis centers), or deaths of the individual (medical examiners). The information provided by DAWN is limited to drug abuse cases which are treated, medically or psychologically, in a participating hospital or crisis center. Even in a standard Metropolitan Statistical Area (SMSA) in which all hospital emergency rooms participate, the only abuse cases reported by DAWN are those in which the abuser or someone in contact with the abuser perceives a problem requiring assistance from a reporting modality. All drug abuse related deaths, however, which occur in a county with a participating medical examiner/coroner will be included in DAWN data.

For the purpose of this study, the following definitions were adopted:

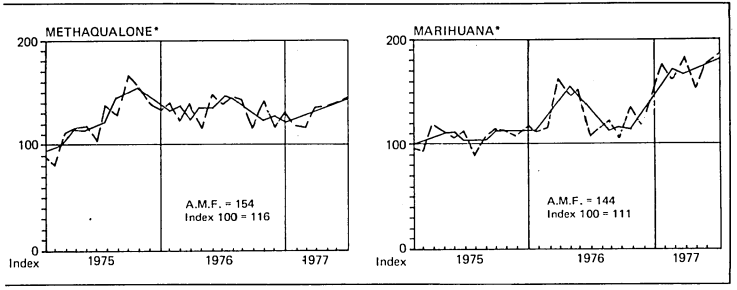
1. *Drug Abuse* was defined as the non-medical use of a substance for any of the

Drug Abuse Trends As Shown By **DAWN** Data
January 1975 - June 1977

A.M.F. = Average Monthly Frequency
—— 3 month moving average
– – Index number



*Source: *DAWN Quarterly Report, April - June 1977*



following reasons: psychic effect, physiological dependence, and attempted or successful self-destruction. For the purposes of this definition, non-medical use means:

a. The use of prescription drugs in a manner inconsistent with accepted medical practice.
b. the use of OTC (over-the-counter) drugs contrary to approved labeling.
c. the use of any other substance (heroin, marihuana, peyote, glue, aerosols, etc.) considered non-medical, and which should be reported with the exceptions of alcohol, caustics, household poisons and other hazardous material, which should be reported only if used in conjunction with another drug, e.g., barbiturates/alcohol, clorox/Diazepam, etc.

Psychic effects include: euphoria, high, kicks, mood alteration, alleviation of unhappiness, sexual enhancement, trips, drug experiences, including experimentation and use for pleasure and fulfillment, use for social or recreational purposes or because of peer pressure.

2. A *drug involved death* may be either:
   a. A *drug induced death* caused by a drug "overdose" where a toxic level is found or suspected, or a death caused by a drug reaction such as an immune reaction or,
   b. A *drug related death* in which a drug(s) is present and is a contributing factor, but not the sole cause of death.

Any incident involving a drug abuse episode or a drug-related death is reportable.

Source of Data

The reporting facilities are concentrated in 24 SMSA's. Of the 24 SMSA's, 20 were "saturated" which indicates an effort was made to solicit participation of all emergency rooms and medical examiners in the DAWN system. In 3 SMSA's (New York, Chicago and Los Angeles), facilities were randomly selected, drawing a sample equal to about 50% of all ER visits occurring within the SMSA.

DEA Use of DAWN

Project **DAWN** data is currently being used within DEA for drug control and scheduling purposes; for following specific drug trends on a regional or local basis (see chart, above and left) for measuring the effectiveness of a drug control action and for allocating resources and staff relative to specific drug problems. Specific examples of the field application of **DAWN** include the following:

- **DAWN** data indicated excessive abuse of Dilaudid in the Philadelphia SMSA. Following the arrest of several "script" doctors in the Philadelphia area, **DAWN** data reflected a noticeable decrease in Dilaudid mentions. Dilaudid ranked second in frequency of drug mentions prior to the arrests and eighth afterwards.
- **DAWN** data about PCP was one of the indicators that assisted Federal and local law enforcers in the identification and elimination of a clandestine laboratory operation in Detroit, Michigan.
- An increase in the **DAWN** mentions for methadone in Texas served to alert area law enforcement agencies to the extent of methadone trafficking there. Independent investigators verified the **DAWN** findings.
- **DAWN** provided some of the first indications that Mandrax, a foreign made methaqualone product, was appearing on the drug abuse scene in this country.

Who Uses DAWN?

Government agencies (DOD, NIDA, FDA) State and local law enforcement agencies, pharmaceutical firms, Single State Agencies,

DAWN VI: SMSA's and Facilities

SMSA's	
Atlanta, GA	Minneapolis, MN
Boston, MA	New Orleans, LA
Buffalo, NY	New York, NY
Chicago, IL	Oklahoma City, OK
Cleveland, OH	Philadelphia, PA
Dallas, TX	Phoenix, AZ
Denver, CO	Norfolk, VA
Detroit, MI	San Antonio, TX
Houston, TX	San Diego, CA
Indianapolis, IN	San Francisco, CA
Kansas City, KA MO	Seattle, WA
Miami, FL	Washington, D.C.

Number of Facilities (DAWN VI)	
Hospital Emergency Room (ER)	778
Medical Examiner/Coroner (ME)	111
Crisis Centers	23
Total Facilities	912

State and local drug abuse authorities and private organizations have used DAWN data or have requested access to it. Generally it is used to assess the drug abuse problem and follow the trends of the changing abuse patterns.

Even though DAWN Phase VI has been modified somewhat in SMSA and facility coverage, the overall program, at the Federal level, still represents one of the most comprehensive drug abuse data gathering indicator networks in size and scope. This system has assisted various government agencies and a number of state, local and private organizations to quantitatively and qualitatively evaluate a general or specific drug abuse problem.

An example of DEA's emphasis on Federal/State cooperation was recently demonstrated in New Hampshire. January 6, 1978, marked the beginning of a new era for DAWN when Governor Meldrim Thomson, Jr. of New Hampshire authorized the implementation of a statewide drug abuse data gathering program patterned after the DAWN System. This action is significant as it represents the forerunner of a larger DEA program to encourage other states to develop Mini-DAWN systems.

The United States Air Force Drug and Alcohol Branch, Social Actions Division, Human Resources Development, Headquarters, Pentagon has incorporated DAWN data into a drug abuse indicator evaluation system. This evaluation will be distributed to all major commands so that base commanders can initiate various types of countermeasures depending upon the level of drug abuse in their areas.

DAWN data was used extensively in preparing the barbiturate study requested by the Office of Drug Abuse Planning and by the Food and Drug Administration in preparation for the amphetamine hearings conducted in December, 1977.

Project DAWN can enable U.S. authorities to evaluate drug abuse problems as seen by medical, social and governmental indicators. It can provide system-wide and regional profiles for types of drug abuse and the abusers themselves. It can enable planners to prepare for the future, as well as providing action agencies the means to detect and react to developing problems.

Analyses of this sort can allow for evaluation of the impact of alternative strategies in specific communities. The availability of comparable information for more than one community will assist our efforts to understand causal relationships and thus permit more accurate programmatic emphasis and direction of resources.

It is important to note that the DAWN data is interpretive and should not be used by itself. DEA and NIDA have attempted to use it in conjunction with the other information available from a variety of sources, including state and local laboratory reports, other epidemiology studies and actual first-hand investigations. The system is used as a means to assist the officials and others concerned with the problems of drug abuse to identify the parameters of the drug abuse phenomenon.

DAWN represents a continuing and dynamic effort that will be constantly reviewed and modified to obtain more precise information upon which regulatory decisions can be based.

Additional Information on DAWN

Requests for additional information or specific data should be directed to:

Mr. Joseph B. Murphy
Chief, Information Systems Section
Office of Compliance & Regulatory Affairs
Drug Enforcement Administration
Washington, D.C. 20537

The Controlled Substances Act

Schedules of Controlled Substances

Schedule I substances. Drugs in this schedule are those that have no accepted medical use in the United States and have a high abuse potential. Some examples are heroin, marihuana, LSD, peyote, mescaline, psilocybin, the tetrahydrocannabinols, ketobemidone, levomoramide, racemoramide, benzylmorphine, dihydromorphine, morphine methylsulfonate, nicocodeine, and nicomorphine.

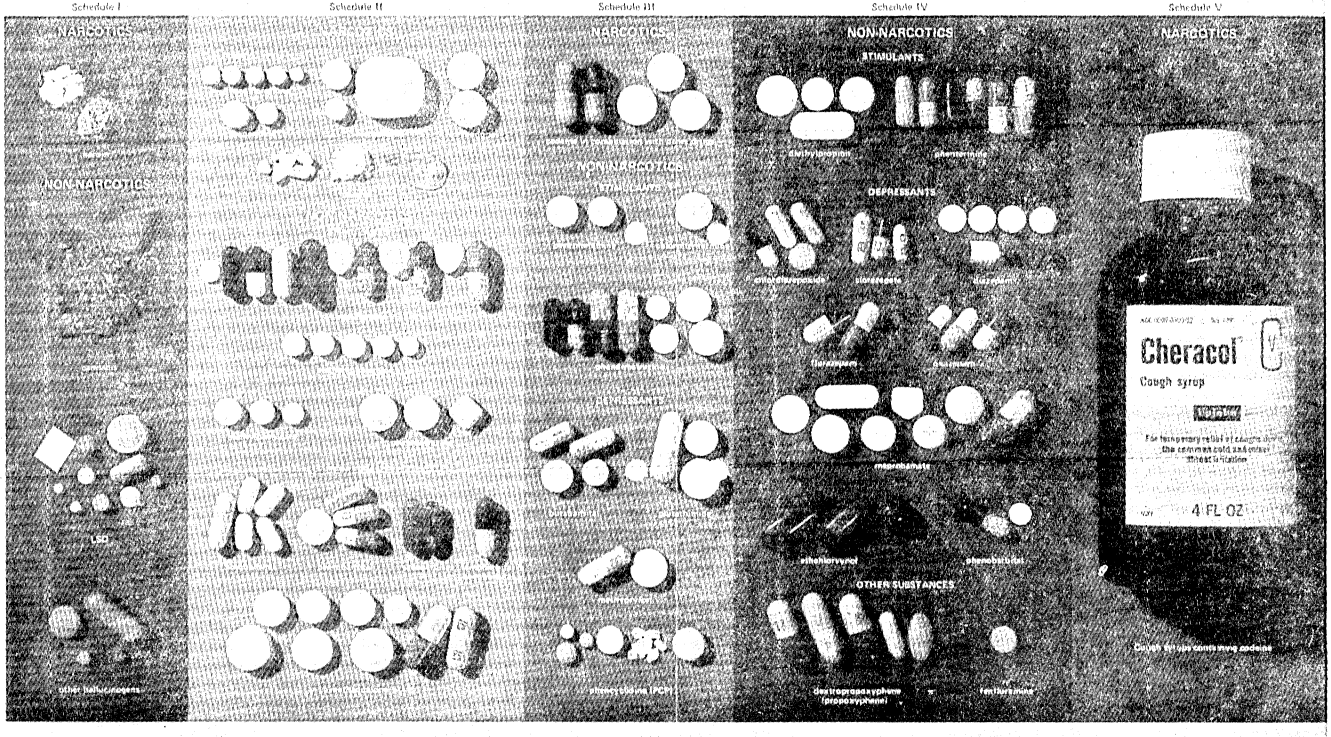
Schedule II substances. The drugs in this schedule have a high abuse potential with severe psychic or physical dependence liability. Schedule II controlled substances consist of certain narcotic drugs and drugs containing amphetamines or methamphetamines as the single active ingredient or in combination with each other. Examples of Schedule II controlled substances are: opium, morphine, codeine, hydromorphone, methadone, pantopon, meperidine, cocaine, oxycodone, anileridine, oxymorphone; and straight amphetamines and methamphetamines. Also in Schedule II are phenmetrazine, methylphenidate, amobarbital, pentobarbital, secobarbital, and methaqualone.

Schedule III substances. The drugs in this schedule have an abuse potential less than those in Schedules I and II and include compounds containing limited quantities of certain narcotic drugs and nonnarcotic drugs, such as: derivatives of barbituric acid, except those that are listed in another schedule, glutethimide, methyprylon, chlorhexadol, phencyclidine, sulfondiethylmethane, sulfonmethane, nalorphine, benzphetamine, chlorphentermine, chlortermine, mazindol, and phendimetrazine. Paregoric is in the schedule as well.

Schedule IV substances. The drugs in this schedule have an abuse potential less than those listed in Schedule III and include such drugs as: barbital, phenobarbital, methylphenobarbital, chloral betaine, chloral hydrate, ethchlorvynol, ethinamate, meprobamate, paraldehyde, pentaerythritol chloral, methohexital, fenfluramine, diethylpropion, and phentermine.

Schedule V substances. The drugs in this schedule have an abuse potential less than those listed in Schedule IV and consist of preparations containing moderate, limited quantities of certain narcotic drugs, generally for antitussive and antidiarrheal purposes, which may be distributed without a prescription order.

Commonly Encountered Controlled Substances



This chart has been prepared with the assistance of the Office of Compliance and Regulatory Affairs.

Regulatory Requirements

Schedule	Registration	Recordkeeping	Distribution Restrictions	Dispensing Limits	Security	Manufacturing Quotas	Import/Export		Manufacturer/Distributor Reports to DEA	
							Narcotic	Non-narcotic	Narcotic	Non-narcotic
I	Required	Separate	Order forms	Research use only	Vault/safe	Yes	Permit	Permit	Yes	Yes
II	Required	Separate	Order forms	Rx: written or EDP	Vault/safe	Yes	Permit	Permit	Yes	Yes
III	Required	Readily retrievable	Records required	Rx: written or oral, with medical authorization, refills up to 5 times in 6 months	Secure storage area	No (or Schedule drugs limited by Schedule II quota)	Permit	Declaration	Yes	No
IV	Required	Readily retrievable	Records required	Rx: written or oral, with medical authorization, refills up to 5 times in 6 months	Secure storage area	No	Permit	Declaration	No	No
V	Required	Readily retrievable	Records required	OTC (Rx only if limited by MD practice)	Secure Storage area	No (or Schedule drugs limited by Schedule II quota)	Permit to import, declaration to export	Declaration	Yes (Triplicate only)	No

Federal Trafficking Penalties

CSA Schedule	Type of Drug	First Offense			Second Offense		
		Maximum Imprisonment (years)	Maximum Fine (thousands of $)	Minimum Parole (years)	Maximum Imprisonment (years)	Maximum Fine (thousands of $)	Minimum Parole (years)
I	Narcotic	15	25	3	30	50	6
	Non-narcotic	5	15	2	10	30	4
II	Narcotic	15	25	3	30	50	6
	Non-narcotic	5	15	2	10	30	4
III	Narcotic	5	15	2	10	30	3
	Non-narcotic	5	15	2	10	30	3
IV	Narcotic	3	10	1	6	20	2
	Non-narcotic	3	10	1	6	20	2
V	Narcotic	1	5	0	2	10	0
	Non-narcotic	1	5	0	2	10	0

For simple possession of any controlled substance: First offenders may receive up to one year, $5,000 fine, or both, and if under 21 may receive up to one-year probation and thereafter motion court for expungement of all records; second offenders may receive up to 2 years, $10,000 fine, or both.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, FEBRUARY 1, 1979

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The committee met, pursuant to call, at 10:07 a.m. in room 5110, Dirksen Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senators Nelson, Bumpers, Stewart, Weicker, Hatch, Hayakawa, and Boschwitz.

Also present: Gerald D. Sturges, professional staff member; Stanley A. Twardy, Jr., minority counsel; and Judith K. Hillegonds, staff assistant.

Senator NELSON. We will resume the hearings this morning with a panel of witnesses consisting of Dr. John Adriani, Department of Health and Human Resources, office of Charity Hospital at New Orleans; Mr. Morris Boynoff, pharmacist, Mendocino, Calif.; Dr. William T. Beaver, associate professor of pharmacology and anesthesia, Georgetown University Schools of Medicine and Dentistry; and Dr. Michael Newman, internist, Washington, D.C.

If you gentlemen would all join at the witness table, we would take your presentations one at a time and then each of you may comment on any other's testimony as you desire.

Gentlemen, the committee is very pleased to have you here this morning and appreciates your taking the time from your very busy schedules to come and testify on this pending matter.

I would ask Dr. Adriani to present his statement first unless you had some particular order in which you wanted to proceed.

It is nice to see you again. Dr. Adriani, and you may proceed and present your statement. Let me say for purposes of the hearing record, we are happy to have you or any of the other witnesses comment on any of the statements made by previous witnesses. Yesterday, Dr. Moertel presented very strong testimony based upon studies done at the Mayo Clinic and reached a very strong conclusion about Darvon, which is set forth on the last page of his statement. At some stage, when you have completed all your testimony, I would like to have your comment on his conclusions.

Go ahead, Dr. Adriani.

STATEMENTS FROM A PANEL CONSISTING OF: JOHN ADRIANI, M.D., DEPARTMENT OF HEALTH AND HUMAN RESOURCES, OFFICE OF CHARITY HOSPITAL AT NEW ORLEANS, LA.; MORRIS BOYNOFF, PHARMACIST, MENDOCINO, CALIF.; WILLIAM T. BEAVER, M.D., ASSOCIATE PROFESSOR OF PHARMACOLOGY AND ANESTHESIA, GEORGETOWN UNIVERSITY SCHOOLS OF MEDICINE AND DENTISTRY, WASHINGTON, D.C.; AND MICHAEL A. NEWMAN, M.D., INTERNIST, WASHINGTON, D.C.

Dr. ADRIANI. Good morning. It is a pleasure to be here once again. As you can see from my statement I was here November 24, 1970, to discuss the same subject we are discussing today, but from a little different point of view.

Senator NELSON. For purposes of the record, Dr. Adriani, would you give a little bit of your background, so that those who read these hearings will know your background, including your service as chairman of the American Medical Association Council on Drugs?

Dr. ADRIANI. I am emeritus professor of surgery (anesthesiology) at Tulane University School of Medicine. I am still active in the departments of pharmacology and anesthesiology at the Louisiana State University School of Medicine and a consultant in anesthesiology and pharmacology in the Department of Health and Human Resources of Louisiana and consultant in various hospitals in New Orleans and still on the staff at the Charity Hospital.

I have appeared before this committee in the past. On one occasion I appeared in my own behalf, while I was chairman of the council of drugs of the AMA. At that time we discussed various things. One of the things we discussed at that time was the publication of a drug compendium. You were very much interested in the publication of such a book on drug information—you had the feeling that doctors did not get enough drug information; the schools did not have enough input and doctors were using drugs empirically.

I agree with you on that. We still have that problem, although it seems to be correcting itself. I am still active, not retired, but I have given up the chairmanships of the various departments I held at Tulane, LSU and Charity. I was the chairman of the anesthesia department at Tulane, at LSU and chief of the anesthesiology service at Charity Hospital for 35 years.

I am also on two advisory panels of the Food and Drug Administration; one on the evaluation of topical analgesic drugs and the other on oral cavity preparations.

As I said before, my statement starts off with the fact that I was here in 1970. At that time, we were talking about analgesics, particularly propoxyphene. As I recall it the question that was at issue was the matter of the Government, particularly the Armed Forces, spending a premium amount of money for Darvon when other drugs that were more effective could have been used and were much less expensive. The issue of lack of effectiveness was fairly well emphasized.

Now, my experience with Darvon goes back when they first began to evaluate it, as an investigational drug. I could not see from the

study that we did that it had any marked advantage over anything else that we were using in the line of analgesics and I advised them of this. In any case, my advice was not accepted.

My feeling on effectiveness is the same way today and has not changed. In addition, the Lilly laboratories also prepared an intravenous solution to be used instead of Demerol for anesthesia in drip form. Since Demerol was a narcotic under restriction and Darvon was not, this would have solved a problem. We found that we had variable results. Sometimes we got marked response of respiration from the drug and had to reverse it with antinarcotics. This dosage form was abandoned.

Our experience as far as efficacy is concerned is that Darvon is not an effective drug. It is pretty well established that it is far less effective than aspirin. Aspirin is one of the best analgesics we have. Most of the analgesia obtained from Darvon is from a placebo effect. Darvon works when it is combined with other analgesics such as aspirin or APC.

At that time (1970) efficacy was at issue. Today, safety is at issue. The attitude that most of us adopted was that even if it does not do any good it does not do any harm. Then occasional cases began to appear in the literature where patients had taken doses in excess of 100 milligrams and developed convulsions and died.

In addition to that, the drug was thought to be nonhabit forming. It was shown prior to release of the drug (1957) that it did relieve some of the withdrawal symptoms of patients who were habituated to and dependent on narcotics. It does have narcotic qualities and today, individuals who are narcotic drug-dependent seem to like it and take it.

For awhile there we had a problem with Darvon because the addicts were taking it intravenously. They dissolved the hydrochloride salt and were taking it intravenously. A less soluble form, the napsylate salt was made. That step has reduced problems arising from intravenous use.

We have now the problem of patients taking it orally over long periods of time getting cumulative effects, and of drug-dependent subjects who need more than the usual doses. These doses are apparently toxic. There are fatalities among drug-dependent persons as a result of overdosage.

Today it is not only a question of efficacy, Mr. Chairman. We also have the question of safety and dependency. The question is, is the risk involved in its use worth the benefit that the drug has? There are other drugs that are safer, more effective, and less expensive. Actually there is really no need to have this drug.

I do believe the popularity of the drug is due to the fact that it was widely promoted. It is much more expensive than aspirin and other analgesics and not as good. We have been able to control the use of it at Charity Hospital because we have it under restriction just as we do narcotics and the doctor has to write a prescription for Darvon in the same manner as he has to for other narcotics.

Senator NELSON. Does Charity permit the use of Darvon?

Dr. ADRIANI. In some cases but the number is small.

Senator NELSON. What kind of a case is it that justifies the use of Darvon?

Dr. ADRIANI. None. Some of the orthopedic surgeons use it.

Senator NELSON. Pardon me?

Dr. ADRIANI. Some of the orthopedic surgeons use it when they treat fractures. There are those who feel if you use aspirin, aspirin causes bleeding in the stomach and Darvon does not and, therefore, they prescribe it instead.

Senator NELSON. But Dr. Moertel just said he could not think of any target group that should use Darvon; that if there is a problem with aspirin there is acetaminophen, and there is codeine. I take it there is no target population for the use of Darvon. Do you?

Dr. ADRIANI. I agree with him, but the impression exists that Darvon can be used in place of aspirin and then you do not have to worry about the bleeding problem which is not the problem they have made it out to be.

Senator NELSON. How does that square with the situation in which—I do not have the figures present—I am told a very substantial percentage of the propoxyphene seen in the marketplace is there in combination form, either with acetaminophen or with aspirin, so those who are turning to Darvon for that alleged reason and prescribing the combination product are giving the aspirin anyway.

Dr. ADRIANI. That is right. I do not agree with those who prescribe it and their reasons for using it. As far as I am concerned, I have not prescribed the drug since I stopped investigating it before it was marketed. The last time I appeared before this committee in reference to Darvon I remarked that my wife was with me and she had a fracture in the kneecap. She was in the hotel with a cast. Her doctor had given her Darvon for pain. I felt, as far as I was concerned, that whatever effect she was getting was from a placebo effect and not from the Darvon.

We have known all along that the efficacy of this drug has been in doubt. The main thing we are concerned with now is the matter of safety, and that is a very important issue.

So, the question is to determine what we are going to do about a drug like this. When do we really need it? Actually, if it were taken off the face of the earth, medical practice would not suffer. I do not know of any situation where a patient cannot be treated because we do not have Darvon. There are other drugs we must have. If we have a man with heart failure and do not have digitalis, we are "stuck". We need digitalis, but Davron does not fall in that category. It is not a drug that we really need.

Since it is not as safe as originally believed, it is not innocuous and is falling into the hands of individuals who are getting it for illicit use. My feeling is that a stronger restriction should be imposed on its availability to patients, either by having it in schedule II or by taking the drug off the market completely, one or the other.

The problem seems to be greater in drug-dependent persons. There are some things that we know now that were not known before about the drug. Two ladies mentioned to me they had taken Darvon and had cocktails served to them afterward and they became acutely ill. This is a central nervous system depressant that has an additive effect with alcohol. That is not generally known and has not been told to patients.

As far as I am concerned, I can see no need for the drug.

We have a welfare program in Louisiana and the most expensive item and most widely prescribed drug in the program, until recently, has been Darvon. The Secretary of Health and Human Resources Administration of Louisiana spoke to me about this. I told him Darvon could be dispensed with and is no longer a drug that the State supplies free. A year ago they did the same thing with some drugs because the bill was tremendous and the budget could not stand it. They took them off the market and we thought we would hear about it, particularly from the State Medical Society but nothing was said and apparently nothing will be said, so far as I know, about Darvon. This was implemented just several weeks ago.

Senator NELSON. You took it out of the welfare program in the State of Louisiana?

Dr. ADRIANI. Yes.

Senator NELSON. That is to say you will not reimburse for it?

Dr. ADRIANI. That is right. If a doctor wants to prescribe it, the patients pay for it.

Senator NELSON. One of the problems cited yesterday by one of the witnesses, more than one as a matter of fact, was that prescription drugs are reimbursable and that nonprescription drugs are not. This witness felt that maybe inducing some doctors to prescribe Darvon, which is reimbursable even though it is not a good analgesic, simply saves the patient some money. Whether or not this is a fact, I do not know.

Dr. ADRIANI No; I think it is the fact that doctors have been brainwashed that Darvon has some superior quality and are not familiar with the fact that it is a very feeble analgesic. When a drug is added to the hospital formulary, it is done by the Pharmacy and Therapeutics Committee. We had to fight to keep Darvon off. Means nothing. Can't remember what I said but it is not important. Codeine has been used and is much more effective than Darvon and certainly aspirin is much more effective. Codeine and aspirin is a very useful combination.

Senator BUMPERS. Mr. Chairman, one question. I was not here yesterday and I am curious. The press has reported the dangers and how many people have died in a day or year from Darvon. What is there about Darvon that makes it more dangerous than aspirin?

Dr. ADRIANI. Well, as I say, it is a central nervous system depressant.

Senator BUMPERS. As I look at the ingredients about the only thing it has that aspirin does not have is caffeine and propoxyphene.

Dr. ADRIANI. Yes. Recent evidence shows that it is a breakdown product that is harmful. Every drug we take is either carried to the liver where it is transformed to another chemical that is less harmful or excreted by the kidney. Occasionally some of the byproducts of a drug are more harmful than the parent compound. The transformation is supposed to reduce the toxicity but with Darvon the toxicity increases.

In the case of aspirin the detoxification occurs very quickly to harmless products. They have found that Darvon is metabolized to a compound called nor-propoxyphene. This has greater toxic effects than Darvon and certain aftereffects. It affects the central nervous system and causes convulsions. It accumulates in the body if you keep taking it. It is not eliminated right away. We refer to the time a drug stays

in the body as the half-life. Nor-propoxyphene has a long half-life—70 hours. If you take three or four capsules a day a cumulative effect results until you reach a point where you have a lethal dose circulating and in the tissues.

Senator BUMPERS. Thank you, very much.

Dr. ADRIANI. My recommendations are summarized at the end of my statement.

The drug could be under stricter controls and placed in schedule II.

It is possible to maintain standards of good medical practice without propoxyphene; therefore, manufacture could be discontinued.

There is no medical justification for continuing its use as an analgesic because it has no therapeutic advantage over other drugs of similar potency that merit its being prescribed for relieving pain.

There will probably be some "static" so to speak, from the medical profession because once doctors have a drug and you take it away from them they claim the Government is coming in and telling them how to practice medicine. When some regulatory agency says we are going to remove a drug from the market, it should do so with concurrence of the medical community. We did this with the amphetamines. The Commissioner of Food and Drugs called in experts and we decided with him how amphetamines should be handled; that they should be resultated. The indications allowed were published in the Federal Register. For a regulatory agency, that is the Government, to come in and say we are going to make this drug no longer available, I am afraid there will be many complaints—maybe not justifiable, but there will be complaints.

Senator NELSON. Well, I guess you answered the question. In general, from your statement, you agree with what Dr. Moertel from the Mayo Clinic said yesterday as to his conclusions.

Dr. ADRIANI. Yes.

Senator NELSON. Thank you, very much, Dr. Adriani. Any questions?

Senator HAYAKAWA. Doctor, thank you for your testimony. Our staff has dug up a statement that you made in 1968 and may I quote:

"The nonaddictive agents such as propoxyphene and other analgesics should be used in the postoperative period for pain relief."

Now, can you reconcile this statement with your statement today that there has been doubt concerning the effectiveness of this drug as a mild analgesic since its introduction?

Dr. ADRIANI. I am sorry. I did not get the last part of your question.

Senator HAYAKAWA. Today you are saying there has been some doubt concerning the effectiveness of this drug as a mild analgesic since its introduction.

In 1968, you apparently did not have these doubts that you are expressing pretty much based on research conducted since 1968.

Dr. ADRIANI. Well, with the work that we did we did not find that the drug was any more effective than other analgesics and was less effective. I do not know if I still have the correspondence in my file and it has been quite a number of years now—1956 or 1957 when I did it, but I said that I could not see any point in marketing this drug, that I did not think it had any particularly therapeutic value.

Senator HAYAKAWA. But what I am quoting is your statement that propoxyphene and other analgesics should be used in the postoperative period for pain relief. These are your own words, Doctor, in 1968.

Dr. ADRIANI. In 1968?

Senator HAYAKAWA. Yes, in an article in Anesthesia and Analgesics, on drug dependence, an article you wrote with Dr. Morgan on drug considerations.

Senator NELSON. May I refresh your memory? You may recall in the hearings in 1970 in which you testified——

Dr. ADRIANI. Yes.

Senator NELSON [continuing]. I would have to look back in the record, but the fact was discovered subsequently that propoxyphene is addictive and was not known in 1970. In 1970, one of the arguments for Darvon was that unlike codeine, which might have addictive properties, Darvon did not, and therefore as to that particular problem Darvon was preferable.

Dr. ADRIANI. Yes.

Senator NELSON. In the past 8 years it has been clearly demonstrated—what was not known then—that it is addictive.

Dr. ADRIANI. Yes.

Senator NELSON. The only issue in our hearings in 1970, as I recall it, was the issue of effectiveness, in which all of the expert witnesses testified as did you that it was less effective.

Dr. ADRIANI. That is right.

Senator NELSON. Less effective than aspirin or acetaminophen.

Dr. ADRIANI. Now you are referring to an article that I wrote using analgesics in drug-dependent persons, is that right?

Senator HAYAKAWA. Drug dependency is a consideration; yes. It was on drug dependency.

Dr. ADRIANI. It was an article on drug dependency and I have always advocated that if we know that a patient is drug-dependent we do not use a narcotic or any drug that we know that produces dependency. We do not want to get him back on drugs that cause dependency.

At that time, the addiction liability of propoxyphene was minimal. There seemed to be some discussion that it was but not significantly so, and we did not consider it addicting like codeine.

Generally, most addicts start with codeine and move over to Demerol and then something else stronger. I had a former pupil who became dependent on codeine. This man stayed with codeine all the time, which is unusual. In relieving pain in patients who we know were drug dependent and are no longer dependent; they have been cured, so to speak; we stay away from addicting drugs or we do not give them anything. A drug like propoxyphene at that time seemed to be indicated.

Senator HAYAKAWA. I understand at that time the addictive quality that you say exists in propoxyphene had not been clearly established; is that what you are saying?

Dr. ADRIANI. That is right.

Senator HAYAKAWA. Thank you, very much.

Senator NELSON. Any other questions?

Thank you.

Senator BUMPERS. How much caffeine, or how many milligrams of caffeine are in an ordinary cup of coffee?

Dr. ADRIANI. I think it is 30 milligrams, I am not sure.

Senator BUMPERS. Thank you.

Senator NELSON. Thank you, Dr. Adriani.

Dr. ADRIANI. There is a typographical error in my statement. There are 32 milligrams of caffeine and in the Darvon compound I have 32 or something like that.

Senator NELSON. The printed record will be corrected to show 32 milligrams in your prepared text, which will be printed in full in the record at this point.

[The prepared statement of Dr. Adriani follows:]

STATEMENT OF JOHN ADRIANI, M.D., PROFESSOR PHARMACOLOGY AND ANESTHESIOLOGY, LOUISIANA STATE UNIVERSITY SCHOOL OF MEDICINE; CONSULTANT PHARMACOLOGY AND ANESTHESIOLOGY, DEPARTMENT OF HEALTH AND HUMAN RESOURCES OF LOUISIANA, NEW ORLEANS, LA.

DEXTROPROPOXYPHENE (DARVON)

Mr. Chairman: I appeared before this Committee on November 24, 1970, and testified on matters pertaining to the efficacy of certain internal analgesics, one of which was propoxyphene, the subject of today's hearings. Propoxyphene was introduced and marketed under the trademark name Darvon by the Lilly Laboratories in 1955. There has been doubt concerning the effectiveness of this drug as a "mild" analgesic since its introduction as a prescription item for oral use. Parenteral dosage forms are not available. Propoxyphene is chemically allied to methadone, a narcotic that is equipotent to morphine on milligram for milligram basis and with approximately the same degree of liability for causing physical dependence. Propoxyphene was described as a non-narcotic analgesic as far as therapeutic efficacy and addiction liability was concerned. It did not appear to have the propensity for causing physical dependence in nondrug dependent persons. It was known that it provided some degree of relief from withdrawal symptoms in persons manifesting physicial dependence to narcotics. The National Academy of Sciences—National Research Council Review Panel on effectiveness of drugs for the relief of pain, found propoxyphene to be less effective than is implied by claims of the manufacturer. On a milligram for milligram basis, propoxyphene was alleged to be equal to codeine in intensity and duration of analgesic action. The Panel found, however, that 65 mg of propoxyphene was equivalent to approximately 30–40 mg of codeine in analgesic potency. The Panel also concluded that 32 mg propoxyphene, in most instances, was no more effective than a placebo. Claims that propoxyphene has fewer side effects than codeine cannot be justified if effective doses of the two drugs are compared.

Beaver, in reviewing the literature on mild analgesics (Beaver, A.P.: American Journal of Medical Sciences 251, p. 576. 1966) noted that studies comparing dextropropoxyphene with aspirin or APC, propoxyphene 32.5 (65 mg) showed it to be consistently inferior to aspirin 325 mg or 650 mg or APC (Aspirin Phenacetin Caffeine) mixture. No convincing evidence has been introduced since this review that any way establishes the superiority of 65 mg doses of propoxyphene over 2 tablets of either aspirin or APC compound used alone.

Propoxyphene is generally combined with other analgesics. Apparently, it is not able to "stand alone" as an analgesic and must be fortified with other drugs to be effective. The original Darvon compound preparation contained 32 mg of propoxyphene, 327 mg of aspirin and 165 mg of phenacetin and 32 mg of caffeine. Darvon compound (65) contained the same amount of aspirin, phenacetin and caffeine and double the amount of propoxyphene. Darvon ASA contains 65 mg of propoxyphene and 325 mg of aspirin, the equivalent of 1 aspirin tablet. Other combinations are available also but none appear to have any superiority to the combination with aspirin. These added drugs were included in the form of pellets in the propoxyphene (Darvon) capsule.

Although there has been doubt about its effectiveness, little has been said about the safety of the drug. From time to time isolated case reports have appeared in the literature of fatalities from propoxyphene when doses in excess of 100 mg were ingested. Recently there has been a marked upswing of the number of adverse reports from the effects of the drug and reports of fatalities from

its use. Although propoxyphene is listed as a "non-narcotic analgesic", it is capable of producing both psychic and physical dependence. Most of the individuals dependent upon the drug have a history of abuse of other drugs. Drug dependent users used to remove the aspirin pellet from the capsule of Darvon compound (propoxyphene hydrochloride with aspirin), dissolved the propoxyphene and used it for intravenous injection to obtain a euphoric effect. Propoxyphene hydrochloride is soluble in water. This practice was obviated by using an insoluble form of the salt of propoxyphene; namely the napsylate.

The reported cases of dependence upon propoxyphene obviously does not present a true picture of the problem because it does not account for the total number of addicts; yet, relatively speaking, the risk of dependence in non-drug dependent persons of propoxyphene appears to be low compared in non-dependent individuals to morphine and meperidine. The Committee on Problems for Drug Abuse of the Notional Academy of Sciences, National Research Council, and other groups have suggested that the term non-narcotic be deleted from advertising by manufacturers since its significance is misinterpreted. The designation "non-narcotic" does not mean that a drug does not produce dependence. It is a term with a legal connotation that indicates neither special narcotic prescriptions are required nor other narcotic controls are imposed prescribing the drug. The fact that propoxyphene hydrochloride (Darvon) was not subjected to the Federal Narcotic Control, plus the fact that it was widely promoted and the impression created that it was innocuous, to a large extent, explains the voluminuos sales of this analgesic. Americans spent over $140,000,000 in 1977 for Lilly manufactured Darvon and Darvon combinations products. The napsylate (Darvon-N Lilly) which was recently introduced is more stable than the hydrochloride. Because of differences in molecular weight, a dose of 100 mg of napsylate is required to provide the amount of propoxyphene equivalent to 65 mg of the hydrochloride. The pharmacologic effects of both salts are similar.

Propoxyphene has been one of the most frequently prescribed drugs in the Louisiana State Medicaid and Welfare Programs. It is now no longer on the list of drugs the State furnishes without cost. At Charity Hospital (an 1800 bed general hospital), where the drug has been controlled since its admission to the Hospital Formulary List, only 7000 units were prescribed in 1978. Reservations about the efficacy of propoxyphene continue to be expressed. In a recently published double-blind study of single doses of propoxyphene, aspirin and other oral analgesics in patients with cancer, Moertel and associates (Moretel, C.G. et al: New England Jour. Med. 286, 813, April 13, 1972) were unable to demonstrate that even 65 mg of propoxyphene was significantly superior to a placebo. In this study, aspirin was the most effective analgesic tested.

Until recently, the attitude towards Darvon has been one of complacency and indifference even though there has been doubt about efficacy all along because the drug was considered safe. The feeling has been "it may not do much good but it does not do any harm". Now, the question of safety has come sharply into focus and there is considerable concern about its continued use.

Propoxyphene is not without adverse effects. In non-dependent individuals, approximately 0.5% of the reactions that occur are minor consisting of nausea, vomiting, drowsiness, rash and vertigo. Hallucinations and disorientation are rare but have been observed. The drug may also cause encephalopathy in patients with diminished liver function. The frequency of adverse effects varies with dosage. There is no evidence that truly analgesic doses of propoxyphene are less harmful than equal analgesic doses of other drugs.

An increasing number of cases of ingestion of lethal and nearly lethal doses of propoxyphene is being reported. In general, the symptoms of overdosage are similar to those resulting with other narcotic drugs. Various degrees of respiratory, central nervous system and circulatory depression are usually present. On the other hand, convulsions, seldom seen with narcotics, as well as coma, have been reported and deaths have resulted. Death usually results from hypoxia accompanied by pulmonary edema and cardiac failure. Propoxyphene toxicity can be treated with narcotic antagonists, such as Naloxone.

The dependence to propoxyphene in narcotic dependent persons is now well documented. It is substantially less intense than that seen with morphine or heroin but nonetheless it does occur. Physical dependence has been observed particularly with high doses. Some physicians and pharmacologists have suggested that dependence would be more frequent if the drug were administered in high enough doses to provide effective analgesia. Orally administered propoxyphene

is reported to be widely abused by adolescents since propoxyphene preparations have been reformulated to eliminate the pellets in the propoxyphene in capsules. Abuse by intravenous injection seems to be on the decline. The possibility of convulsions increases as the dose is increased. Dependent persons require large doses to obtain the desired effect and this dose may be the lethal one for certain individuals. The margin of safety is narrow when doses exceeding 100 mg are used.

According to recent information released from the Drug Enforcement Agency, propoxyphene leads all other restricted prescription drugs in the United States in drug related deaths. Because propoxyphene is of so little value as an analgesic and becoming more widely abused and is not as safe as has been assumed, it is urged that the drug be controlled more strictly and placed in Schedule II or removed from the market. According to a report prepared by the Health Research Group (200P3 N.W., Washington, D.C.) during 1977 alone there were 589 propoxyphene related deaths reported to this group which collects data from areas covering only ⅓ of the population of this country. This number is greater than the number resulting from the use of heroin. Since the question of safety is now before us and since there is so much doubt about its efficacy as an analgesic, the following conclusions, suggestions and recommendations can be made concerning propoxyphene:

1. The drug could be under stricter controls and placed in Schedule II.
2. It is possible to maintain standards of good medical practice without propoxyphene; therefore, manufacture could be discontinued.
3. There is no medical justification for continuing its use as an analgesic because it has no therapeutic advantage over other drugs of similar potency that merit its being prescribed for relieving pain.

Senator NELSON. Next, we will hear from Dr. William T. Beaver, associate professor of pharmacology and anesthesia at Georgetown University.

It has been hard to hear Dr. Adriani from that microphone. Perhaps you can push it about 6 inches back.

STATEMENT OF WILLIAM T. BEAVER, M.D.—Resumed

Dr. BEAVER. I will do the best I can, Senator. I appreciate being invited back to talk after the almost 10 years since I was here last.

During the last 15 years, I have had repeated occasion to review the literature on propoxyphene. In 1965, I wrote a review of the clinical pharmacology of the mild analgesics, which included a substantial section on propoxyphene. In 1966 and 1967, I served as a member of the Panel on Drugs for Relief of Pain, Drug Efficacy Study of the National Academy of Sciences-National Research Council and was the primary reviewer on propoxyphene and its combinations for the Panel. On November 24, 1970, I appeared before this subcommittee to discuss the relative merits of various mild analgesics in the relief of pain, and a portion of this testimony was devoted to a critique of propoxyphene, or Darvon.

From 1969 to 1976, I served as a consultant for the Food and Drug Administration, primarily on matters related to analgesic drugs and the design and interpretation of controlled clinical trials for drug efficacy. While serving as a consultant for the FDA, I prepared a special critique of the efficacy of propoxyphene based on my review of the published literature and the New Drug Applications for various propoxyphene products. This critique, submitted to Henry E. Simmons, M.D., Director, Bureau of Drugs, plus recommendations for revision of the propoxyphene labeling served as the basis for the re-

labeling of propoxyphene products which occurred in 1972. In 1976, I assisted the FDA in revising the propoxyphene labeling to reflect increased medical awareness (Finkel et al., 1976; McBay and Hudson, 1975) of the incidence of fatal overdose with propoxyphene alone and in combination with other central nervous system depressants.

I subsequently served as a FDA consultant to their Controlled Substances Advisory Committee in the matter of the advisability of scheduling Darvon under the Controlled Substances Act. The committee recommended placing propoxyphene products in schedule IV. The Department of Health, Education, and Welfare concurred in this recommendation, and, in February 1977, the Drug Enforcement Administration issued an order to that effect. Since 1976, I have continued to follow the literature on propoxyphene, in part because I am chairman, Advisory Panel on Analgesics, Sedatives and Anti-inflammatory Agents for the 1975–80 revision of the United States Pharmacopeia.

Now, concerning the general pharmacologic properties of propoxyphene, propoxyphene or dextropropoxyphene (Darvon) is structurally related to the potent narcotic methadone and is itself a narcotic in all pharmacologic and toxicologic respects.

It produces the full spectrum of pharmacologic effects in animals and man characteristic of the narcotics, and these effects are selectively reversed by the specific narcotic antagonist naloxone. Quantitatively, however, propoxyphene is substantially less potent on a milligram basis than narcotics such as morphine, hydromorphine (Dilaudid) and methadone.

In addition, high doses of propoxyphene have certain excitatory properties not noted with most other narcotics which, while they tend to discourage deliberate abuse of propoxyphene, make convulsions a common feature of propoxyphene overdose in addition to the usual narcotic overdose manifestations of respiratory depression and coma.

In relation to propoxyphene's analgesic efficacy, which seems to be one of the major subjects that has been talked about thus far in these hearings, on reviewing those studies which have appeared in the interim, I find little necessity to modify my evaluation of the efficacy of dextropropoxyphene which appeared in 1966 which I presented in my testimony on November 24, 1970.

Propoxyphene compared to placebo: In addition to the studies cited in my 1966 review, eight additional controlled analgesic studies have confirmed that a 65 milligram dose of propoxyphene hydrochloride or the equivalent 100 milligram dose of propoxyphene napsylate is statistically significantly superior to placebo in relieving postoperative and trauma pain, postpartum uterine cramping, postpartum episiotomy pain, pain subsequent to oral surgery in outpatients and chronic pain of mixed etiology.

A couple of studies have also succeeded in demonstrating a statistically significant difference between placebo and either 32 milligrams of propoxyphene hydrocholoride or the equivalent 50 milligram dose of propoxyphene napsylate; but these obviously represent threshhold or marginally effective doses of propoxyphene, the analgesic effect of which doses can only very rarely be measured in even the most sensitive analgesic assays.

Five additional studies since my original testimony have also confirmed the existence of a significant positive slope for the dose-response curve of propoxyphene using various graded doses of the hydrochloride salt from 32 to 200 milligrams and/or the equivalent doses of the napsylate salt of 50 to 300 milligrams.

In my opinion, the above cited studies alone and in conjunction with those I have previously reviewed, prove beyond any doubt that propoxyphene hydrochloride in doses of 65 milligrams and higher or propoxyphene napsylate in doses of 100 milligrams and higher have some analgesic activity in patients with pain of a wide variety of etiologies.

Indeed, since propoxyphene produces narcotic-like responses in all pharmacologic tests with which I am familiar, can produce drug dependence of the classic narcotic type and produces an overdose syndrome characteristic of narcotics, I would find it impossible to explain how the drug could possibly *not* be an effective analgesic at some dose level.

Now, several double-blind studies which ostensibly meet the minimum criteria for a controlled clinical trial of analgesic efficacy have not demonstrated a statistically significant difference between the analgesic effect of 65 milligrams of propoxyphene hydrochloride and a placebo treatment. There are a number of possible explanations for this state of affairs, and most of them hinge on an understanding of the concept of assay sensitivity as it applies to clinical trials of analgesics.

Because of the multiplicity of known and unknown variables which affect the course of a patient's pain and its response to analgesics, and because there is no satisfactory measure of a patient's pain other than the patient's own subjective reports of this experience, analgesic clinical trials vary greatly in their ability to demonstrate the efficacy of even known effective analgesics. That is, they vary widely in their assay sensitivity. Therefore, unless an analgesic clinical trial contains an internal measure of assay sensitivity that demonstrates that the trial is capable of measuring an analgesic effect of the magnitude anticipated to result from administration of the test drug, for example propoxyphene, a negative finding concerning the efficacy of the test drug has no meaning.

Most of the clinical trials which did not distinguish propoxyphene from placebo either did not contain a measure of assay sensitivity or were clearly insensitive in that they also could not distinguish known analgesics, for example, codeine or aspirin from placebo.

Furthermore, since single doses of propoxyphene 65 milligrams are almost certainly less effective than the usually used doses of the mild analgesic standards, codeine 65 milligrams, aspirin 650 milligrams, acetaminophen 650 milligrams or two APC tablets, an oral mild analgesic study may have adequate assay sensitivity to demonstrate a statistically significant difference between one or more of these standards and the placebo, while still not being able to identify the less substantial analgesic effect of propoxyphene 65 milligrams as statistically significant. That is my interpretation of the results of Dr. Moertel's study which was presented in the New England Journal of Medicine and which he discussed yesterday at these hearings.

Now, concerning the comparisions of propoxyphene with other mild analgesics, first propoxyphene compared to codeine. Since propoxyphene is a "weak" narcotic, oral codeine is the most appropriate standard of comparison.

My review of the literature in 1966 led me to the conclusion that propoxyphene hydrocholoride was definitely less potent on a milligram basis than codeine, my best estimate of the relative potency of the two drugs being that propoxyphene is one-half to two-thirds as potent as codeine.

In the interval, no definitive relative potency assay comparing graded doses of the two drugs has appeared, but the results of a few more recent clinical studies are generally consistent with the above estimate.

Two other studies designed to evaluate the analgesic effect of two consecutive doses of each of the study medications, suggest that propoxyphene napsylate 100 milligrams is approximately equianalgesic to codeine 60 milligrams, but deficiencies in data presentation make it impossible for me to judge the validity of this interpretation.

Mr. Chairman, I am leaving out the reference citations which back up all of these statements that I have been making because I assume they will appear in the printed record of my statement.

Senator NELSON. Yes; they will appear in the record.

Dr. BEAVER. Now, propoxyphene compared to aspirin, acetaminophen or APC: The results of studies I reviewed in 1966 and a few more recent studies comparing propoxyphene hydrochloride 65 milligrams or propoxyphene napsylate 100 milligrams with aspirin 650 milligrams, acetaminophen 650 milligrams or 1,000 milligrams, or APC 2 tablets are consistent with the evaluation which I presented to this subcommittee in 1970; namely, that propoxyphene at recommended doses is certainly no more, and probably less, effective than usually used doses of aspirin, acetaminophen or APC.

Concerning the efficacy of propoxyphene as a constituent of drug combinations. Relatively little propoxyphene is used as a single-entity analgesic. Well over 80 percent of the prescriptions for propoxyphene products are for combinations of propoxyphene with acetaminophen, APC, or aspirin.

The rationale for these combinations is the same as that which underlies combinations of codeine and other yet more potent narcotics with these same antipyretic-analgesics; namely, production of more intense analgesia than can be provided by using a single agent and reduction of side effects by reducing the dose of any one analgesic.

Although experimental evidence to substantiate these theoretical rationales is far from ideal or complete, there is a substantial body of evidence from well-controlled clinical analgesic trials to indicate that combinations of appropriately chosen doses of antipyretic-analgesics with narcotics do, in fact, achieve these objectives.

The slopes of the log dose-response curves of analgesic drugs are relatively flat, with the result that even successive doubling of the dose produces only modest increments of analgesic effect.

Narcotics and antipyretic-analgesics such as aspirin are known to produce analgesia by different mechanisms, and the simple additive

effect of a narcotic and an antipyretic-analgesic given together is often significantly greater than the analgesia achieved by doubling the dose of either drug administered alone.

Furthermore, antipyretic-analgesics probably exhibit a ceiling of analgesic effect at about the usually used doses—650 to 1,000 milligrams—and the usefulness of higher doses may also be limited by increased incidence of adverse effects and serious cumulative toxicity.

Increasing doses of codeine, propoxyphene and other narcotics are associated with a progressively increasing incidence and severity of gastrointestinal and central nervous system side effects and increased risk of drug dependence.

The problem of providing adequate pain relief in the face of the above noted limitations of currently available analgesics may sometimes be circumvented by combining an optimal dose of an antipyretic-analgesic with an orally effective narcotic in a modest dose which is reasonably safe and well-tolerated.

Older relevant studies for both codeine and propoxyphene combinations are cited in my 1966 review. There are a few more recent studies which appear to demonstrate a significant increase in analgesic effect produced by the addition of propoxyphene to acetaminophen.

Dr. Moertel and his associates showed a small increase in the effect of aspirin 650 milligrams produced by the addition of propoxyphene napsylate 100 milligrams, but the difference was not statistically significant.

Now I would like to briefly touch on the adverse effects of propoxyphene. There are really three types and it is important to think clearly about this issue, to keep these types of adverse effects separate in one's mind, because they have different implications in relation to drug abuse.

These three types are adverse effects seen at recommended therapeutic doses; adverse effects seen in overdose and the issue of drug dependence on propoxyphene.

In relation to adverse effects of propoxyphene at therapeutic dose levels or recommended dose levels, which is propoxyphene hydrochloride 65 milligrams or propoxyphene napsylate 100 milligrams, propoxyphene produces an extremely low level of adverse effects.

As a matter of fact, most studies are unable to demonstrate a significantly higher incidence of adverse effects with these doses of propoxyphene than with a placebo.

When large enough groups of ambulatory patients are studied to demonstrate any difference in terms of adverse effects between therapeutic doses of propoxyphene and placebo, the adverse effects consist of a very low incidence of nausea and drowsiness.

Considering the extraordinarily large use of propoxyphene products, there is extremely little in the entire literature which indicates that the drug in recommended therapeutic doses can produce any serious adverse effects, and even minor adverse effects seem to occur only infrequently.

Now, concerning the toxicity of propoxyphene in overdose: As noted above and as is amply attested to by numerous individual case reports and several epidemiologic studies; propoxyphene, like any

other narcotic, can be lethal in ovedose; although the full extent of this problem was not appreciated until relatively recent.

Back in the late 1960's we were aware of only occasional cases of overdose. I can recall that, when I reviewed the New Drug Application in 1971 for the FDA, I really could only scratch up a handful of lethal cases of propoxyphene overdose from its introduction until that time. My guess is that the very substantial increase which has appeared over the course of the last several years does not necessarily reflect a true, very substantial increase in the number of propoxyphene related deaths, but rather that dependable analytical methodologies to demonstrate propoxyphene in the bloodstream was only really developed and became available in the late 1960's and the early 1970's.

When you start looking for something with a useful tool, you begin to find it, and that may account for the discrepancies.

In regard to the dependence liability of propoxyphene, since propoxyphene is pharmacologically a narcotic, it has some ability to produce drug dependence of the narcotic type, and this has been recognized since before the drug was marketed.

Propoxyphene can produce the classic triad of psychic dependence, physical dependence and tolerance, and, in those patients who are able to tolerate high enough doses to result in substantial physical dependence, a narcotic-type abstinence syndrome has been observed on withdrawal.

"Street abuse" of the drug clearly occurs, as does dependence secondary to therapeutic use. However, in my opinion, relative to the extremely wide use of propoxyphene, the demonstrated incidence of serious deliberate abuse of the drug to experience its mood effects is not great and is certainly less than is the case with potent narcotics.

Senator NELSON. May I ask a question. Dr. Beaver? Yesterday, the witnesses who testified from North Carolina and Oregon were divided on the question of whether or not intentional overdose was a serious question.

One of the witnesses felt very strongly that a good many, over half of the deaths that occurred, were not drug abusers or those who intentionally overdosed themselves, based on the study of the stomach contents and so forth. So his argument was not because it was being abused—any drug can be abused—but because people were getting overdoses unintentionally.

Dr. BEAVER. Let me clarify the point. I believe what the medical examiner from Oregon was pointing out was that he felt that many of these deaths were associated with accidental overdose as opposed to deliberate suicidal overdose. That is the distinction I think he was making. Neither of those things is the same as what I am talking about, which is the deliberate use of the drug to experience the mood effect; that is to say, drug abuse considerations.

Senator NELSON. I was only saying, if it was the Oregon witness, that it is his feeling that most of the deaths were not intentional overdosages.

Dr. BEAVER. Were not suicidal, but neither suicides nor accidents are specifically related to the use of the drug for mood effect.

Senator NELSON. I understand.

Dr. BEAVER. What I am talking about here is the degree to which people seek this drug out and take it to get "high" and that sort of thing, the same way heroin is abused. I am pointing out that that type of abuse of the drug, from what I can tell, is relatively low, and it was predicted to be low on the basis of the work that was done back in the 1950's for very particular reasons.

I digress from my testimony because it is important to explain this. Physicians are very sensitive about this. They are almost paranoid about the issue of inducing drug dependence in their patients with the narcotics they give them. So there has been a tremendous effort over the years to develop narcotics which would not have that effect, good analgesics which do not have a narcotic-type abuse liability.

Darvon was, in part, a result of this line of work. When it was tested at Lexington, it turned out it did have the narcotic-type abuse liability, but only to a very limited degree. If you gave small doses to the post-addicts they would report it as being narcotic, but they said, "It is very weak, give me more." You give a higher dose and they say, "Yes, that feels better, but give me some more." So you give a higher dose and some subjects would have convulsions. Propoxyphene has a toxicity which discourages deliberate abuse in the sense of people taking it to get "high" and, of course, the whole focus at that time was to avoid such problems.

You see, the problem that this brings along with it is that you have a drug which may be inherently more toxic when somebody takes it in overdose than conventional narcotics. So you have the two-edged sword. You are trying to make a drug that people do not like to abuse, and you do it by making the drug more toxic, but this creates certain other kinds of problems. I am trying to bring out the history of why we are in the situation we are in at the moment.

Senator BUMPERS. Dr. Beaver, you heard Dr. Adriani's response to my question about what the dangers are and he said it is the part of propoxyphene that goes to the liver and becomes nor-propoxyphene and builds up in the liver and stays in the body and cumulatively, the danger is greater than normal analgesics.

Dr. BEAVER. This is a interesting hypothesis and I will mention this further in my testimony. I would point out we know very little about nor-propoxyphene. There are only a couple of studies in the literature on the metabolite when it is given alone to animals. We know essentially nothing about what this material does when given alone to man.

Most of the Darvon overdose deaths which I have read about in reviewing the literature can very adequately be explained simply on the basis that this drug is a narcotic and produces narcotic depression and coma; produces convulsions which makes it harder to treat the overdose and the patient then dies.

The nor-propoxyphene matter is something that has recently come up and represents an interesting pharmacological lead that may, in fact, account for some of the aspects of the poisoning that we have not been able to account for. But one must make the distinction between something which is well established scientifically, in fact, and something that is just an interesting pharmacological lead.

Senator HATCH. Doctor, it is my understanding people are not dying from propoxyphene per se, but from ingesting overdoses of the drug