Now, we had some preliminary discussions with Dr. Finkle hoping that, perhaps in concert with interested members of industry and Government, a more precise evaluation of the dimensions of the problem could be undertaken in the next few years.

I must emphasize these are very preliminary discussions, and there is no guarantee that they will provide answers to these questions, but they are questions which desperately need addressing.

Senator WEICKER. Thank you.

Senator NELSON. Senator Levin?

Senator LEVIN. In 1972 you wrote a letter apparently at the request of FDA at least according to their testimony, "There is no substantial evidence to demonstrate that 65 milligrams of Darvon is more effective than 650 milligrams of aspirin."

I guess that is comparing one Darvon.

Dr. FURMAN. One Darvon to two aspirin.

Senator LEVIN. And the preponderance of evidence indicates it may be somewhat less benefit. Was that true then in your opinion? If so, is it still true?

Dr. FURMAN. By "preponderance of evidence" they meant well-controlled, double-blind, placebo studies, and I think literally that was correct at that time.

Senator LEVIN. And now?

Dr. FURMAN. I think there are studies which compare propoxyphene hydrochloride, 65 milligrams, or napsylate, 100 miligrams, favorably with aspirin but do not demonstrate greater efficacy.

I want to make it abundantly clear that aspirin is a truly remarkable drug—it lowers temperature and it is being used and evaluated for people with coronary heart disease and stroke. We are not embarrassed that propoxyphene and two aspirin tablets are equal.

Senator LEVIN. Are there many people would you estimate now that are using propoxyphene that could get equal results from aspirin?

Dr. FURMAN. That is a very difficult question to answer, Senator, because people who are now relying on propoxyphene for relief and control of pain, by and large, are people who have had access previously to acetaminophen and aspirin. Somehow or other, sooner or later, they got a prescription from their doctor for propoxyphene and have found that propoxyphene or propoxyphene-combined products effectively do the job.

Senator LEVIN. Have you authorized studies, your company that is, comparing the efficacy of aspirin and propoxyphene?

Dr. FURMAN. Yes, sir, we have.

Senator LEVIN. Could you estimate how many of those studies have taken place? Are those double-blind studies?

Dr. FURMAN. Some were. Some of the early studies of propoxyphene compared with aspirin and codeine were double-blind studies. I could not tell you how many, offhand.

Senator LEVIN. Would there be many?

Dr. FURMAN. Several.

Senator LEVIN. Could you furnish us all of the studies you have authorized, all the double-blind studies you have authorized comparing propoxyphene with aspirin and codeine?

Dr. FURMAN. We would be glad to do that.

Senator LEVIN. Thank you.

Senator NELSON. Any other questions?

Senator WEICKER. I would like to point out one thing that might be helpful to describe the relationship between the pharmaceutical manufacturer and the medical profession itself. I am afraid it comes across, at least it did to me in these hearings, that the relationship under consideration is one between a very sophisticated institution such as the pharmaceutical manufacturer and the public as a whole, which might not be in the possession of the knowledge needed to evaluate the product. Yet, in fact, it seems to me that there is a pretty extensive filtering system or jury on the product itself, in terms of the medical profession which must prescribe the drug.

Now certainly there can be no lack of degree or sophistication attributed to that body of society. At the same time, what is the procedure for the use of a drug? Is there a considerable comment made by the physicians themselves—do they ask questions of the manufacturer?

Can you describe that process to us? It is entirely left out of the impression given at these hearings. The general question of safety and efficacy of a drug is an important one. But one must realize that the drug goes out into a marketplace that is comprised of very knowledgeable and sophisticated persons, that is, doctors, who are able to make the types of judgments on the product commensurate with their knowledge.

Can you comment on that?

Dr. FURMAN. In every piece of package literature and every advertisement and every communication where these products are mentioned, we—almost without exception—provide the product labeling which carries the recommended dosage, the indications, the contraindications, and information on treatment of overdosage. These are continually reviewed. As I indicated, we are now in the process of strengthening the part of the package that deals with the management of overdosage.

We bring this to the attention of the physician. Instances of overdose, fatal or not, and overdose information also appear in medical literature.

This literature is scanned by our in-house physicians. We have commercial survey companies that keep their eye on newspapers and other news media for any example of a misuse of propoxyphene.

We make every effort to followup each one and get information. As new evidence of pharmacologic action—good, bad, or indifferent—is received by our scientists and other research laboratories, it is evaluated and shared with the FDA, reported at open scientific meetings, and, when judged appropriate and necessary, is put in the package piece.

Reference was made in one of the hearing days last week that the Physicians' Desk Reference is distributed free of charge by the Pharmaceutical Manufacturers Association. That is not correct. It is distributed by the publisher. The information in the Physicians' Desk Reference is information on products that are approved by the FDA and is in full conformity with FDA requirements as to labeling.

We feel that there is a continual flow of information and resource material available to the physician for the adequate, proper, and safe use of these agents.

Senator WEICKER. In other words, the point I am making here I think there is a local grocery store in Washington that makes the point that the best customer is an educated consumer. We are not talking about the public at large. The real consumer is the physician himself.

Dr. FURMAN. Yes, sir.

Senator WEICKER. Certainly, nobody can ascribe a lack of education to that particular individual as far as this product is concerned. If the product does not work, it seems to me that it would not be prescribed.

We are not talking about a drug that might have just burst on the market in a fit of temporary popularity. We are talking about something on the marketplace for 21 years. Now, if it is no good, why do doctors go ahead and recommend it? I do not understand this, unless there is some sort of a tie-in between the industry and the doctor's prescriptions, and that is illegal. If there is, I want to hear about that.

Dr. FURMAN. I think you put your finger on the answer regarding efficacy. Propoxyphene is out there and it works, and it has enjoyed great usefulness and popularity for more than two decades.

The FDA did not have to ban blood-letting. Somebody last week testified that propoxyphene was essentially a nostrum like ground ram's horn and this sort of nonsense. These nostrums are not perceived as effective by the physician indefinitely. Their patients are sick; and I think, Senator Weicker, you are correct, that this is a useful drug; that the physician is not prescribing it willy-nilly. He is using it. He gets the report from his patient that it works, and he is content it is safe and effective; and that is the reason the drug has been successful for more than two decades.

Senator WEICKER. I would imagine that probably Darvon's days are numbered, not in the sense of what Government can or cannot do to it, but in the sense that people are seeking to discover a better product in the sense of what it can do.

Dr. FURMAN. We, ourselves, will, I hope, come out with a better product; but over the last two decades, as I think Dr. Beaver pointed out, nobody has come up with a better type of centrally acting analgesic.

Senator WEICKER. I gather, to emphasize what you are saying, that you are not claiming that propoxyphene is better than aspirin in all cases.

Dr. FURMAN. No.

Senator WEICKER. I just wanted to make that point. I am very much for consumers as my voting record indicates. However, I think it is very important that the picture be made clear as to what is involved and who is involved in this particular instance, so we do not perceive this to be another case of the corporate world ripping off the man on the street.

There are other factors involved here and a filtering process that makes this situation considerably different than just the normal situation of the consumer and the corporate product.

Dr. FURMAN. I appreciate your comments.

Senator HATCH. On page 3 of Dr. Wolfe's testimony there is a reference to a Danish study concluding Darvon has a small margin

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

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

Senator HATCH. That is right.

Dr. FURMAN. Simonsen.

Senator HATCH. It is on page 3.

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

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

Senator HATCH. Is that the 65-milligram level?

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

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

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

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

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

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

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

olite nor-propoxyphene, when infused into an anesthetized dog, produced delay in conduction—that is to say, heart block—in a dose-related manner; namely, as the dose was increased, the degree of conduction delay was increased. This conduction delay is referred to by cardiologists as heart block.

I submit that anyone with a reasonable knowledge of cardiac physiology would have regarded the abstract sent to the FDA describing this work as containing the essence of the information, the necessary information on which to make a judgment regarding this experimental cardiac effect. I can assure you that the cardiac abnormalities that have been described in the medical literature and individuals taking a fatal overdose indicate that the cardiac problems arise when respiration is depressed or ceases. These people accumulate carbon dioxide in the bloodstream and become depleted of oxygen. This is a bad situation for the heart, and it makes the patient vulnerable to abnormal heart action. When respiratory movements are restored by a mechanical ventilator and the carbon dioxide is washed out of the body and normal oxygenation occurs, the heart abnormality—with rare exception—disappears. This occurs over a timespan of minutes to hours, which precludes any significant change having occurred in the concentration of nor-propoxyphene.

Furthermore, studies by Dr. Tennet in California, in which he administered at least twice the routine dosage of propoxyphene to individuals in a heroin-maintenance program, have shown in such individuals, for a period of more than 2 years, that electrocardiograms taken at 3-month intervals showed no effect whatsoever of the long term use of large doses of propoxyphene.

Our own studies on volunteers equipped with a Holter monitor, which makes a continuous tape recording of the EKG, show that the recommended dose of propoxyphene for periods as long as a week produces no discernible effect on the EKG.

Senator HATCH. Thank you.

Senator NELSON. Anything else?

Senator BAUCUS. I have one question concerning cost. What would be the changes in cost to Lilly if Darvon is rescheduled to schedule II.

Dr. FURMAN. The cost changes?

Senator BAUCUS. Manufacturing costs on a per unit basis.

Dr. FURMAN. Senator, I have no idea. I am sure it would increase manufacturing costs, but this is beyond my area of knowledge and capability. Sorry.

Senator BAUCUS. You have any estimate, any guess?

Dr. FURMAN. It would be the wildest guess, sir. I would not hazard a guess.

Senator BAUCUS. But you do think the cost would increase?

Dr. FURMAN. Oh, yes, I believe so.

Senator BAUCUS. Just a rough guess. Is it a 1-percent increase, 5 percent? Your guess.

Dr. FURMAN. Your guess is as good as mine, Senator.

Senator BAUCUS. Yours is a lot better than mine.

Dr. FURMAN. I am not sure.

Senator BAUCUS. The same line of questioning with respect to consumer costs. Would you expect the market price to increase if Darvon is rescheduled as schedule II?

Dr. FURMAN. Again, I would hesitate to comment on that. It would depend on the manufacturing costs.

Senator BAUCUS. Since manufacturing costs would increase in your judgment although you are not sure to what degree, do you therefore expect the market price of the product to increase?

Dr. FURMAN. I would expect so.

Senator BAUCUS. It would be list price?

Dr. FURMAN. The actual retail price is not determined by us but determined by the retail pharmacist; and that, in turn, is determined by at least what he has to pay the distributor.

Senator BAUCUS. But you would expect the retail price to be higher?

Dr. FURMAN. Well, I cannot conceive of it going down. I guess it would go up.

Senator BAUCUS. Thank you, Mr. Chairman.

Senator NELSON. I certainly do not wish to prolong this, and when you testified and went through page 5 I did not raise the question, but later in a dialog with you Senator Weicker did, so I do not want it to go by without some comment for the record.

In reference to the sentence in your prepared testimony in which you state, "In the final analysis, the true measure of the therapeutic usefulness of a drug is determined in the field of clinical practice," I gather from the dialog between you and Senator Weicker that it was agreed between you that if a drug is widely used in the marketplace, that demonstrates its therapeutic value.

I only want to point out that we have had 12 years of hearings with testimony by distinguished national and internationally known clinicians who would strongly refute that proposition.

I would simply call your attention to the testimony on antibiotics. Even the Journal of the American Medical Association, which has been very careful over the years never to criticize the drug industry, which supports the publication of the magazine, did in 1957 and in subsequent editorials strongly urge doctors to quit prescribing combination antibiotics on the grounds it was a very bad clinical practice. The fact that use of combination antibiotics was widespread did not make it good medical practice.

To argue as so many do that if it is widely used in the marketplace, it must be a good drug is overwhelmingly refuted by the evidence.

Dr. FURMAN. May I respond, Mr. Chairman?

Senator NELSON. Certainly.

Dr. FURMAN. I think your concern and your distrust are understandable, in part justified; but let me point out there are notable exceptions in the antibiotic field. For example, in the treatment of strep fecalis infection and septicemia, combinations of penicillin and streptomycin are extremely effective.

One of the cost-effective anti-infective agents recently approved by the FDA, Bactrim and Septra, is a combination product. The combination of propoxyphene and salicylate makes a very justifiable pharmacologic union in view of the peripheral and centrally acting modalities of these compounds. The analgesia demonstrated in animal experiments—I know of no placebo responders among animals—plus clinical trials tend to make me feel that most physicians using propoxyphene really know what they are doing.

Senator NELSON. I would not want to mention when and where, but I was on a trip to a convention and everybody on the trip got Darvon. Nobody got an aspirin or anything else. He was given Darvon.

On the question of placebo on animals, that may be so, but it is very difficult to explain the false pregnancies that dogs sometimes get.

Dr. FURMAN. Makes it a very interesting business.

Senator NELSON. Thank you very much. I appreciate your taking the time to come. If you have anything you wish to add to the testimony we would be happy to receive it for the record.

Dr. FURMAN. Thank you.

Senator NELSON. Our next witness is Dr. Louis Lasagna, chairman of the Department and Professor of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry.

The committee is pleased to have you come today. Your statement will be printed in full in the record and you may proceed any way you desire. We are already at 12:30, but we need to complete our testimony, so we will proceed.

STATEMENT OF LOUIS LASAGNA, M.D., CHAIRMAN OF THE DEPARTMENT AND PROFESSOR OF PHARMACOLOGY AND TOXICOLOGY, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY

Dr. LASAGNA. My name is Louis Lasagna. I am professor of pharmacology and toxicology and professor of medicine at the University of Rochester School of Medicine and Dentistry. For over a quarter of a century I have engaged in research on analgesic drugs, and have written extensively in this area.

I appreciate this opportunity to share my thoughts with you in regard to the suggestion that propoxyphene constitutes a major drug abuse problem and an imminent hazard to the health of the U.S. public.

Propoxyphene is unquestionably an effective analgesic drug, either when given alone or in combination with such drugs as aspirin or acetaminophen. This judgment was reached by the Analgesic Drugs Panel which I chaired in the late 1960's for the National Academy of Sciences-National Research Council at the request of the FDA Commissioner, and is an opinion still supported by a review today of the world literature on pain-relieving drugs. It is unfortunate that some who are concerned about the euphorigenicity or toxicity of propoxyphene feel constrained to deny the ability of propoxyphene to relieve pain. Millions of patients have taken, and continue to take, propoxyphene for its analgesic properties. No placebo effect can explain its popularity.

It has been known for years that while propoxyphene, like any drug which affects the central nervous system, can be abused by some individuals, the risks of such abuse are minuscule. National and international expert advisory committees have repeatedly taken up this issue since the original marketing of the drug, and have never seen a need to reclassify propoxyphene as a drug with high addiction liability.

More recently, drug-associated fatalities have been observed in individuals taking excessive doses of propoxyphene, especially in combi-

nation with alcohol and other CNS depressants. After an investigation of this new concern, the Eli Lilly Co. revised labeling for propoxyphene and undertook a campaign aimed at acquainting U.S. physicians with this important new information. When HEW recommended to the Justice Department that propoxyphene products should be placed in schedule IV, so far as I know the manufacturer did not oppose the listing.

I believe that both the FDA and the several manufacturers of propoxyphene are cognizant of these new developments concerning this drug and have not shown any reluctance to take appropriate steps to inform the prescribing physician.

The data from the Government-financed drug abuse warning network—DAWN—while far from a perfect representation of national drug abuse problems, nevertheless provides information which contradicts the allegation that propoxyphene abuse is increasing and constitutes an imminent hazard. I have followed the DAWN data for some years because of my interest in drug reporting systems.

The most recent reports available to me—Project DAWN VI and the January-March 1978 DAWN Quarterly Report—show, for example, that there are more yearly mentions of aspirin in emergency room reports—7,212—than of propoxyphene—4,111. The crisis centers in the DAWN system reported a yearly total of 488 propoxyphene mentions, as opposed to 7,243 for heroin/morphine, despite the much smaller number of people exposed to the latter narcotics. Propoxyphene is also mentioned less often than heroin/morphine in medical examiner reports in the DAWN system, with only 486 mentions of all sorts for the entire year.

More important, I believe, is the pattern of decreasing reports for propoxyphene when one looks at the data base recommended by DAWN itself for the best assessment of time trends, that is the so-called consistent reporters. The number of emergency room drug mentions for propoxyphene peaked in October-December 1976 at 892 and has decreased to 753 for the January-March 1978—the most recently analyzed period.

Similarly, the propoxyphene mentions for consistently reporting medical examiners peaked in January-March 1977 at 169 and declined to 125 for the most recently analyzed period, October-December 1977.

I believe that the available data in general support the image that the profession has had of propoxyphene—an analgesic which can be useful in treating people with mild to moderate pain with a minimum of side effects and no significant toxicity unless taken in doses much larger than those recommended for medical use.

Some drug abuse will occur with any analgesic drug. It is of interest, for example, that DAWN reports twice as many mentions in its emergency rooms for aspirin and two-thirds as many for acetaminophen, as for propoxyphene. These two OTC drugs, available to anyone without a prescription, can also, in large doses, produce organ damage and death, even without the ingestion of other drugs. Branding these OTC analgesics as an "imminent hazard," nevertheless, would be as foolish as recommendations to do so for propoxyphene.

The concept that propoxyphene is an excessively expensive and ex-

cessively prescribed analgesic has its supporters, but the proposed remedies for these putative problems would represent a dangerous and ill-advised precedent. Our medical care system should not be politicized by unscientific pressures to abolish a drug, or to impose manufacturing quotas on it whenever a group of individuals object to the extent of use and the cost of a given drug. The implications of yielding to such demands are ominous for medical care. If propoxyphene is banned today, which drug will be doomed for extinction tomorrow? Aspirin? Acetaminophen? Narcotic substitutes for propoxyphene? Valium?

It is appropriate to debate these issues, but I do not believe that a thoughtful and dispassionate analysis of propoxyphene will find it necessary to accuse the FDA or the manufacturer of either apathy or irresponsibility.

I would urge, Senator, that you exert your considerable influence to help convene meetings involving the FDA, the DEA, the relevant scientific advisory groups for these agencies, and representatives of responsible and prestigious professional and patient groups to assess what we know about propoxyphene, to plan studies for obtaining better data on the motivations and circumstances leading to abuse from propoxyphene and other drugs, to consider the implications of encouraging the substitution of other non-narcotic and narcotic analgesics for propoxyphene, and to study the level of information among physicians and patients as to the benefits and risks of propoxyphene and of competing analgesics, and the treatment of accidental or purposeful overdose. Such meetings could identify what educational efforts might be needed to optimize medical care for patients in pain.

Thank you for the opportunity to express these personal opinions.

Senator NELSON. Thank you, Dr. Lasagna. You did not identify for the record the fact that you were as I recall it, Chairman of the NRC Panel on Propoxyphene.

Dr. LASAGNÁ. On Analgesic Drugs.

Senator NELSON. What year was that?

Dr. LASAGNA. That was in the 1960's.

Senator NELSON. 1969, was it? That was before the evaluation under the 1962 act.

Dr. LASAGNA. Yes, sir.

Senator NELSON. Have there been any further evaluations? I forgot to ask Mr. Kennedy under the provisions of the 1962 act as to the effectiveness of Darvon in combination, but are you aware?

Dr. LASAGNA. Well, certainly nothing like the NRC review.

If I may comment, Senator, on that deliberation, if you look at our report for analgesic combinations most of the time we were forced to say that such and such a combination contained an analgesic of known efficacy in standard dosage and we did not know whether the other ingredients present added to or subtracted from that analgesic, but for Darvon compound we were able to say, because there were some studies available, that, in fact, the data supported the notion that propoxyphene added for example to aspirin did give something over and above what aspirin gave of itself.

There were several studies available at the time of our review and there are several I am sure that have been printed since that time and I would be glad to submit those references to you.

Senator NELSON. I would be happy to have the references.

The testimony of Dr. Moertel on his double-blind studies at Mayo Clinic was the addition of a full dose of propoxyphene to aspirin did not in those studies indicate any additional effectiveness.

Now, I do not know how many of these studies there are on that, but I would like to have the number.

Dr. LASAGNA. I might say, Senator, in addition to this being a mucky field—oral analgesic evaluation—imprecise I should say, aspirin is such a good drug that it is not easy to top it, but while there are certainly studies that have been done that failed to show the superiority of the combination and there are others that do show it.

It is a field that is less precise than we would like to have.

Senator NELSON. Any questions?

Senator HAYAKAWA. Is it not true that that which is effective on others, that is some patients, is not effective on others so that there are people for whom let us say aspirin does no good but propoxyphene does and there are people for whom propoxyphene does no good and aspirin does.

Are there not these individual differences?

Dr. LASAGNA. Yes; there are.

Senator HAYAKAWA. I am interested in your statement that while it can be abused, propoxyphene in other words, risks are minuscule; that is the risks occur when people take far more than the recommended dosage. Is that correct?

Dr. LASAGNA. Yes, sir. I had references to two kinds of risk. One is the risk of abusing the drug in the sense we usually mean, taking the drug for kicks. There are some people who use the drug for that purpose; there is another risk in regard to individuals taking more of the drug than is recommended or taking it in combination with other drugs or alcohol.

Senator HAYAKAWA. What concerns me is the attempt to ban one drug after another or to make them more difficult of access.

Aspirin has been shown to be dangerous when abused and acetaminophen is dangerous when abused and valium obviously so. So if propoxyphene is banned today, where do we go next?

This passion for banning seems to indicate a kind of passion that some regulators have of creating an ultimately totally risk-free society which is, of course, beyond human possibility.

Nevertheless, what you are saying is that propoxyphene abuse is decreasing rather than increasing in cases where it does occur; is that correct?

Dr. LASAGNA. At least that is the conclusion I come to on the basis of the data available to me.

Senator HAYAKAWA. I see. Well, I am grateful to you for a not too technical exhibition of this problem and I agree with you that FDA, DEA and the science community should obtain better data on the motivation leading to abuse of the substance. But so far as I am concerned I think like aspirin and many other things like Empirin and Bufferin and everything else, it is a useful substance to have available as one of the many, many substances we might take for relief of pain. There is no one analgesic that is good for everybody, is there?

Dr. LASAGNA. That is right.

Senator HAYAKAWA. Thank you, very much.

Senator NELSON. Any other questions?

Thank you very much, Dr. Lasagna, for taking the time to come here and present your testimony today. We appreciate it very much.

[The prepared statement of Dr. Lasagna follows:]

STATEMENT BY LOUIS LASAGNA, M.D., PROFESSOR OF PHARMACOLOGY AND TOXICOLOGY AND PROFESSOR OF MEDICINE AT THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, N.Y.

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I believe that the available data in general support the image that the profession has had of propoxyphene—an analgesic which can be useful in treating people with mild to moderate pain with a minimum of side effects and no significant toxicity unless taken in doses much larger than those recommended for medical use.

Some drug abuse will occur with any analgesic drug. It is of interest, e.g., that DAWN reports twice as many mentions in its emergency rooms for aspirin and two-thirds as many for acetaminophen, as for propoxyphene. These two OTC drugs, available to anyone without a prescription, can also, in large doses, produce organ damage and death, even without the ingestion of other drugs. Branding these OTC analgesics as an "imminent hazard", nevertheless, would be as foolish as the recommendation to do so for propoxyphene.

The concept that propoxyphene is an excessively expensive and excessively prescribed analgesic has its supporters but the proposed remedies for these putative problems would represent a dangerous and ill-advised precedent. Our medical care system should not be politicized by unscientific pressures to abolish a drug, or to impose manufacturing quotas on it whenever a group of individuals object to the extent of use and the cost of a given drug. The implications of yielding to such demands are ominous for medical care. If propoxyphene is banned today, which drug will be doomed for extinction tomorrow? Aspirin? Acetaminophen? Narcotic substitutes for propoxyphene? Valium?

It is appropriate to debate these issues, but I do not believe that a thoughtful and dispassionate analysis of propoxyphene will find it necessary to accuse the FDA or the manufacturer of either apathy or irresponsibility.

I would urge, Senator, that you exert your considerable influence to help convene meetings invovling the FDA, the DEA, the relevant scientific advisory groups for these agencies, and representatives of responsible and prestigious professional and patient groups to assess what we know about propoxyphene, to plan studies for obtaining better data on the motivations and circumstances leading to abuse from propoxyphene and other drugs, to consider the implications of encouraging the substitution of other nonnarcotic and narcotic analgesics for propoxyphene, and to study the level of information among physicians and patience as to the benefits and risks of propoxyphene and of competing analygesics, and the treatment of accidental or purposeful overdose. Such meetings could identify what educational efforts might be needed to optimize medical care for patients in pain.

Thank you for the opportunity to express these personal opinions.

Senator NELSON. Our final witness is Dr. Bryan S. Finkle, director of the center for human toxicology at the University of Utah Health Sciences Center, and assistant professor of pharmacology-toxicology and pathology.

Your statement will be presented in full in the record, together with your memo which is attached to your statement.

STATEMENT OF DR. BRYAN S. FINKLE, DIRECTOR, CENTER FOR HUMAN TOXICOLOGY AT THE UNIVERSITY OF UTAH HEALTH SCIENCES CENTER AND ASSISTANT PROFESSOR OF PHARMACOLOGY-TOXICOLOGY AND PATHOLOGY

Dr. FINKLE. I would like to point out I have brought copies of my statement, not available earlier and I see the clerk has attended to that.

As you have said, I am Dr. Bryan S. Finkle, director of the Center for Human Toxicology at the University of Utah Health Sciences Center and assistant professor of pharmacology-toxicology and pathology.

I have been continually engaged in forensic toxicology, medico-legal investigation and clinical toxicology for some 22 years. I welcome the

opportunity to present to you a short—I hope no more than about 10 minutes—statement on the toxicology of propoxyphene, and I thank you for this opportunity.

The role of propoxyphene and its major metabolites in medico-legal investigation has been of interest to toxicologists for the past decade. As the availability of the drug and its subsequent prescription by physicians increased so, inevitably, its frequency of occurrence in cases of sudden, unexplained death presented analytical and pharmacological problems for forensic and clinical scientists.

As a direct result of several reports in the early 1970's which indicated an apparent growing involvement of propoxyphene in forensic toxicology cases the Center for Human Toxicology, University of Utah—supported by Eli Lilly & Co. and FDA—under my direction undertook an independent national collaborative study in 1975–76 to assess the role of propoxyphene in post mortem cases and place the drug in perspective against demographic and epidemiological information about the deceased individuals. The study was also designed to evaluate the current laboratory techniques used to detect, identify, and quantitate the drug and its metabolites in biological specimens.

The results of the study, which involved 18 forensic toxicologists, medical examiners, and coroners, was published in the Journal of Forensic Sciences in 1976.

Senator NELSON. Let me ask a question for clarification. On the first page you say the Center for Human Toxicology is supported by Lilly and the FDA.

Are you saying the Center for Human Toxicology is supported by Eli Lilly & Co. and the FDA, or did they support this particular study?

Dr. FINKLE. The latter is correct. Would be that it was the former. I have attached to my statement a reprint of that study for your information and perusal.

Senator NELSON. Is that the one we have here called "Memorandum for the record"?

Dr. FINKLE. No, it is not, Senator. It is a separate document.

Senator NELSON. Very well.

Dr. FINKLE. The principal findings indicated that during the period 1970–75, the number of deaths involving propoxyphene increased each year and at a faster rate than total drug deaths. About half of the 1,022 cases studies were suicides. The deceased were not part of the illegal drug abuse population and had no particular propensity for the use of heroin or narcotics, but were a particular medical population with a marked tendency to hypochondria, chronic minor illnesses, and emotional problems, and misuse of a variety of prescription drugs and alcohol.

It was confirmed that propoxyphene can be a dangerous drug when misused, deliberately or accidentally, but most especially in combination with alcohol and/or other central nervous system depressant drugs. I am not speaking here of the fixed drug combinations in Darvon such as aspirin, but the many other drugs such as barbiturates and tranquilizers and so on which are listed in the table appended as part of this statement.

From a toxicology perspective propoxyphene appeared to be no more dangerous than many other potent drugs available, and that typical of

the modern forensic toxicology scene it presented as a mixed drug, combination phenomenon.

The report also described the potential importance of propoxyphene-metabolite toxicity and noted the need for improved laboratory methods to detect and quantitate the drug.

Since this report other papers have been published which corroborate the findings, and corollary data have been developed through medical examiner reports to the Drug Abuse Warning Network system—DAWN.

An uncritical analysis of DAWN data would indicate that the occurrence of propoxyphene in sudden, unexplained death cases has continued unabated in the last 2 years. In order to inspect the validity of this assumption I undertook a short followup study, with particular reference to those sites which matched DAWN reporting areas and those at which particular case reports were announced.

The appended table shows some of the results and clearly indicates that since 1975 there has been a small but consistent decrease in the number of propoxyphene-associated drug death cases each year. This is an important trend.

Further, it is clear that suicides continue to predominate in this population and that propoxyphene occurs most often in multiple drug deaths in which the particular toxicological significance of propoxyphene and its metabolites is not usually defined.

If the human toxicology of propoxyphene is to be truly described then it is imperative that its role in each case be evaluated, and only reported for statistical purposes in those cases in which it is toxicologically significant. Any other practice will inevitably lead to erroneously inflated case reports and provide a misleading basis for possible public health regulation and drug control. A summary of the findings of this most recent study are attached for your information.

[The summary referred to follows:]

INCIDENCE OF DPX-ASSOCIATED CASES, BY SITE, BY YEAR

Site	Finkle Code	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Alameda County Oakland, CA	0	–	3	3	3	9	11	←		7-10/yr.**	→
Dade City, FL	DCF	–	–	–	2	13	10	11	–	–	–
Dallas City/County	D	–	–	–	14	10	16	12†	6†	11†	11†
Wayne County Detroit, MI	WCD	–	–	–	8	12	24†	32†	17†	14†	16†
Georgia	G	–	1	2	5	6	6	4	–	–	–
Hennepin County, MI	HC	–	–	4	1	1	1	6	–	–	–
Illinois	IL	–	–	–	2	3	9	10	–	–	–
Las Vegas City/County	LV	–	–	–	2	1	2	5	–	–	–
Los Angeles City/County	LA	–	–	–	37	33	63	32	–	–	–
St. Paul, MN	SP	–	–	–	1	2	3	3	–	–	–
New Mexico	NM	–	–	–	–	4	8	11	–	–	–
North Carolina	NC	2	3	2	23 (21*)	23 (21*)	32 (30*)	25 (50*)	34*	36*	31*
Orange County, CA	OC	–	–	–	8	12	15	←		15-20/yr.**	→
Oregon	OR	–	–	–	1	0	0	5	–	40***	21/6 mo***
Philadelphia City/County	PH	–	–	–	25	22	28	38**	25**	25**	⟨20**
San Diego City/County	SD	–	–	–	20	24	23	19†	26†	24†	17†
Utah	UT	–	–	–	–	7	11	2	←	⟨5/yr.	→
Toronto + Ontario	TOR	–	–	–	44	39	46	42	–	–	–
Maryland	MD	–	–	–	–	–	19**	45**	32**	43**	≐40**
Phoenix, Maricopa County	MC	–	–	–	–	8+	18†	28†	10†	16†	15†

Sources (unless otherwise noted): Finkle et al., 1975 survey

*McBay/N.C. memo dated December 19, 1978

**Finkle update memo dated December 21, 1978

†Finkle update January 29, 1979

***Correspondence and Forms 1639, State Medical Examiner, Oregon

revised 1-30-79

Dr. FINKLE. It has been asserted that the number of deaths caused by propoxyphene is now greater than those from heroin. This question was addressed at each of the study sites. At most sites this is simply not true; and in those areas where propoxyphene is detected in unexplained death cases with greater frequency than heroin/morphine this is clearly a function of the dramatic reduction in heroin fatalities in almost all areas of the United States since 1976 and not related to a supposed increase in propoxyphene cases.

Again, this points to a need for careful examination of individual cases before general, epidemiological inferences are drawn.

The report—and this statement—certainly do not exonerate propoxyphene as a safe drug; it is of major concern to all toxicologists. There is no absolutely safe drug, and it is irresponsible to condemn a valuable pharmacological agent before accurate data are available to place its adverse effects in perspective with those of other similar drugs, and current forensic and clinical toxicology experience.

If I might digress; the memorandum to which you referred, Senator, is a report to myself of that study and the principal findings of the followup study. I would now like to add one thing. You will notice that in my view a very important study site is at Dallas City and county, and the Institute for Forensic Sciences at Dallas was included in the followup study and was also in the original study. An important letter was sent to me by Dr. Vincent DiMaio who is the deputy chief medical examiner at that office. The letter came to me too late for inclusion in my prepared statement and I would now like to read it into the record and include it as part of my testimony.

Senator NELSON. Go ahead.

Dr. FINKLE. The letter was originally addressed to Dr. Wolfe in response to a letter Dr. Wolfe sent to Dr. DiMaio. It reads:

I am in receipt of your letter dated December 18, 1978, concerning the Health Research Group's petition to the DEA requesting transfer of propoxyphine to schedule II of the Controlled Substances Act.

It is my opinion that the danger of propoxyphene is overinflated. Propoxyphene like any other drug can kill if misused. Accidental deaths from the use of propoxyphene are rare. Most alleged accidental deaths are drug abuse deaths. Any drug abused is dangerous. More common than drug abuse deaths with propoxyphene are suicides. I do not think that by making propoxyphene difficult to obtain, one will decrease the rate of suicides. One will just change the drug or its use. All one has to do is compare the method of suicides in different areas of the country to realize that access to drugs would make little difference in the suicide rate.

In the latest data from our office propoxyphene accounts for nine deaths; six of these were determined to be suicidal gestures. Along with your letter was a copy of a letter to Joseph Califano, Secretary of Health, Education, and Welfare. This was apparently a public letter released on Tuesday, November 21, 1978. I think your cause might be taken more seriously if in this letter you had not included data that was incorrect.

On page 3, table 2, you list the propoxyphene-related deaths from July 1973 to December 1977. I am afraid that I cannot believe any of the figures in that table. The reason I do not is that for Dallas you indicate that there were 80 such deaths in that period of time. I would like to inform you that from January 1973 to December 1977 in Dallas there was a total of only 30 deaths due to propoxyphene. An additional 25 individuals died of a combination of multiple drugs and also had propoxyphene detected in their blood.

If you include both, then the maximum number of cases would be 65 rather than 80.

Senator NELSON. Let me interrupt you. I thought the first figure was 30 and the combination deaths were 25. That ought to be 55, not 65.

Dr. FINKLE. That is correct, Senator.

In fact, in a number of the mixed drug deaths the propoxyphene was present only in small, therapeutic amounts and was only incidental.

Part of the epidemic of propoxyphene deaths being reported is that until fairly recently many toxicology laboratories were deficient in their ability to detect propoxyphene. Therefore, such deaths were being missed for many years. Some of the cases in which the propoxyphene was taken intravenously were considered as morphine deaths. To go on:

I am afraid that I also doubt your contention on page 2 of your letter that propoxyphene was associated with more deaths than heroin/morphine in the first half of 1977.

While methods of deaths from propoxyphene are readily available and used by toxicology laboratories, many of these laboratories are unable to detect morphine in the blood. Thus, they will miss rapid deaths from morphine or heroin injections and if so, and some propoxyphene is found they may attribute such deaths to propoxyphene rather than morphine.

I want to include this letter because Dallas was part of the followup study that I conducted. Essentially, the facts that are in this letter are supported by my findings when I went to Dallas and examined their cases file by file, and I would like to further state that in my opinion the medical/legal investigation system in Dallas City and County is one of the best in the country and that their toxicologists and their toxicology laboratory certainly ranks in the top three or four in the country.

I ended my statement by saying that the current trend indicates a decrease in propoxyphene cases and that this is important. Further, it is clear that suicides continue to dominate in these cases.

Several questions must be addressed. Most victims are suicides; can legislation prevent suicidal ingestion of multiple drugs?

What needs to be done to better understand the toxicology of multiple drug usage? Research is desperately needed in this area. What is the role of alcohol—the drug of abuse and death—in combination with propoxyphene?

If this analgesic is removed from medical use, what will take its place?

Are there safe, toxicologically benign alternatives? This is a critical question to be answered before any precipitant action is taken. Few medical-science problems are solved by negative action; there is need to maximize the medical assets of propoxyphene and minimize its liabilities through decisions based on clinical and pharmacological understanding, and with a refined, focused system designed to carefully monitor its performance prospectively.

The Center for Human Toxicology staff have carried out retrospective studies at great labor and cost on four or five different agents to date. If only there were established a refined system of monitoring these drugs and some other like-drugs prospectively as they were used in the medical context by physicians and patients, then this kind of retrospective panic data gathering with all its loose ends would not be necessary, and we would be in a much better position to provide your committee, FDA, and other agencies with the kind of information you truly need.

I am not an advocate for propoxyphene or any other particular drug, but a biomedical scientist who recognizes a critical need for a method of effective evaluation of human toxicology. DAWN is a valuable but blunt tool, not designed for this purpose but so often misused because it is the only instrument available. It is not good enough alone for toxicologists' purposes. A cool, continuous examination of toxicological facts as they become available through a prospective monitoring system is required, together with improved laboratory practice and applied research. The overriding purpose should be better medicine and improved public health through the dispassionate work of medical examiners, coroners, and toxicologists. They are the ombudsmen of public health, and their professional efforts deserve better than ill-considered interpretation resulting in hasty, self-defeating legal regulation.

Thank you.

Senator NELSON. Thank you very much, Dr. Finkle. We appreciate your taking the time to come and present your testimony today. It will be included in full in the record, of course, along with the memorandum you have submitted and along with the other documents.

I want to thank all of the witnesses very much for appearing here today.

As I said earlier, the record will be kept open for 2 weeks for submission of any additional testimony or documents.

Again, thank you very much.

That will conclude the hearings.

[Whereupon, at 1:05 p.m., hearings in the above-entitled matter were concluded.]

[The prepared statement of Dr. Bryan S. Finkle, together with a memorandum for the record, biographical data, and letter to Dr. Sidney M. Wolfe, follow:]

Statement To The U.S. Senate Select Committee On Small Business
Chairman: Senator Gaylord Nelson

THE MEDICO-LEGAL TOXICOLOGY OF PROPOXYPHENE

I am Dr. Bryan S. Finkle, Director of the Center for Human Toxicology at the University of Utah Health Sciences Center; and Assistant Professor of Pharmacology-Toxicology and Pathology.

Gentlemen:

I welcome the opportunity to present to you a short (10 minute) statement on the current toxicology of propoxyphene and I thank you for this privilege.

The role of propoxyphene and its major metabolites in medico-legal investigation has been of interest to toxicologists for the past decade. As the availability of the drug and its subsequent prescription by physicians increased so, inevitably, its frequency of occurrence in cases of sudden, unexplained death presented analytical and pharmacological problems for forensic and clinical scientists. As a direct result of several reports in the early 1970's indicating an apparent growing involvement of propoxyphene in forensic toxicology cases the Center for Human Toxicology, University of Utah, (supported by Eli Lilly and Company and F.D.A.) under my direction undertook an independent national collaborative study in 1975-76 to assess the role of propoxyphene in postmortem cases and place the drug in perspective against demographic and epidemiological information about the deceased individuals. The study was also designed to

evaluate the current laboratory techniques used to detect, identify and quantitate the drug and its metabolites in biological specimens. The results of the study, which involved eighteen forensic toxicologists, medical examiners and coroners, was published in the Journal of Forensic Sciences in 1976. The principal findings indicated that during the period 1970-75, the number of deaths involving propoxyphene increased each year and at a faster rate than total drug deaths. About half of the 1,022 cases studied were suicides. The deceased were not part of the illegal drug abuse population and had no particular propensity for the use of heroin or narcotics, but were a particular medical population with a marked tendency to hypochondria, chronic minor illnesses and emotional problems,and misuse of a variety of prescription drugs and alcohol. It was confirmed that propoxyphene can be a dangerous drug when misused, deliberately or accidentally, but most especially in combination with alcohol and/or other central nervous system depressant drugs. From a toxicology perspective propoxyphene appeared to be no more dangerous than many other potent drugs available, and that typical of the modern forensic toxicology scene it presented as a mixed drug, combination phenomenon. The report also described the potential importance of propoxyphene-metabolite toxicity and noted the need for improved laboratory methods to detect and quantitate the drug.

Since this report other papers have been published which corraborate the findings, and corollary data have been developed through Medical

Examiner reports to the Drug Abuse Warning Network system (DAWN). An uncritical analysis of DAWN data would indicate that the occurrence of propoxyphene in sudden, unexplained death cases has continued unabated in the last two years. In order to inspect the validity of this assumption I undertook a short follow-up study in the past three months, at some of the 1975 sites in my prior study, with particular reference to those which matched DAWN reporting areas and those at which particular case reports were announced. The appended table shows some of the results and clearly indicates that since 1975 there has been a small but consistent decrease in the number of propoxyphene-associated drug death cases each year. This is an important trend. Further, it is clear that suicides continue to predominate in this population and that propoxyphene occurs most often in multiple drug deaths in which the particular toxicological significance of propoxyphene and its metabolites is not usually defined. If the human toxicology of propoxyphene is to be truly described then it is imperative that its role in each case be evaluated, and only reported for statistical purposes in those cases in which it is toxicologically significant. Any other practice will inevitably lead to erroneously inflated case reports and provide a misleading basis for possible public health regulation and drug control. A summary of the findings of this most recent study are attached for your information.

INCIDENCE OF DPX-ASSOCIATED CASES, BY SITE, BY YEAR

Site	Finkle Code	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Alameda County Oakland, CA	0	–	3	3	3	9	11	←		7-10/yr.**	→
Dade City, FL	DCF	–	–	–	2	13	10	11	–	–	–
Dallas City/County	D	–	–	–	14	10	16	12†	6†	11†	11†
Wayne County Detroit, MI	WCD	–	–	–	8	12	24†	32†	17†	14†	16†
Georgia	G	–	1	2	5	6	6	4	–	–	–
Hennepin County, MI	HC	–	–	4	1	1	1	6	–	–	–
Illinois	IL	–	–	–	2	3	9	10	–	–	–
Las Vegas City/County	LV	–	–	–	2	1	2	5	–	–	–
Los Angeles City/County	LA	–	–	–	37	33	63	32	–	–	–
St. Paul, MN	SP	–	–	–	1	2	3	3	–	–	–
New Mexico	NM	–	–	–	–	4	8	11	–	–	–
North Carolina	NC	2	3	2	23 (21*)	23 (21*)	32 (30*)	25 (50*)	34*	36*	31*
Orange County, CA	OC	–	–	–	8	12	15	←		15-20/yr.**	→
Oregon	OR	–	–	–	1	0	0	5	–	40***	21/6 mo***
Philadelphia City/County	PH	–	–	–	25	22	28	38**	25**	25**	(20**
San Diego City/County	SD	–	–	–	20	24	23	19†	26†	24†	17†
Utah	UT	–	–	–	–	7	11	2	←	(5/yr.	→
Toronto + Ontario	TOR	–	–	–	44	39	46	42	–	–	–
Maryland	MD	–	–	–	–	–	19**	45**	32**	43**	≈40**
Phoenix, Maricopa County	MC	–	–	–	–	8+	18†	28†	10†	16†	15†

Sources (unless otherwise noted): Finkle et al., 1975 survey

*McBay/N.C. memo dated December 19, 1978

**Finkle update memo dated December 21, 1978

†Finkle update January 29, 1979

***Correspondence and Forms 1639, State Medical Examiner, Oregon

revised 1-30-79

It has been asserted that the number of deaths caused by propoxyphene is now greater than those from heroin. This question was addressed at each of the study sites. At most sites this is simply not true; and in those areas where propoxyphene is detected in unexplained death cases with greater frequency than heroin (morphine) this is clearly a function of the dramatic reduction in heroin fatalities in almost all areas of the United States since 1976 and not related to a supposed increase in propoxyphene cases. Again, this points to a need for careful examination of individual cases before general, epidemiological inferences are drawn.

The report (and this statement) certainly do not exonerate propoxyphene as a safe drug; it is of major concern to all toxicologists. There is no absolutely safe drug, and it is irresponsible to condemn a valuable pharmacological agent before accurate data are available to place its adverse effects in perspective with those of other similar drugs, and current forensic and clinical toxicology experience.

Several questions must be addressed: Most victims are suicides; can legislation prevent suicidal ingestion of multiple drugs? What needs to be done to better understand the toxicology of multiple drug usage? Research is desperately needed in this area. What is the role of alcohol (THE drug of abuse and death) in combination with propoxyphene? If this analgesic is removed from medical use what will take its place? Are

there safe, toxicologically benign alternatives? This is a critical question to be answered before any precipitant action is taken. Few medical-science problems are solved by negative action, there is a need to maximize the medical assets of propoxyphene and minimize its liabilities through decisions based on clinical and pharmacological understanding; and with a refined, focussed system designed to carefully monitor its performance prospectively.

I am not an advocate for propoxyphene or any other particular drug, but a biomedical scientist who recognizes a critical need for a method of effective evaluation of human toxicology. DAWN is a valuable but blunt tool, not designed for this purpose but so often misused because it is the only instrument available. It is not good enough alone for toxicologists' purposes. A cool, continuous examination of toxicological facts as they become available through a prospective monitoring system is required; together with improved laboratory practice and applied research. The overriding purpose should be better medicine and improved public health through the dispassionate work of medical examiners, coroners and toxicologists. They are the ombudsmen of public health and their professional efforts deserve better than ill-considered interpretation resulting in hasty, self-defeating legal regulation.

MEMORANDUM FOR THE RECORD

January 29, 1979

Subject: PROPOXYPHENE: TOXICITY STUDY 1978-79

Further to current reports concerning the incidence of propoxyphene in postmortem medico-legal investigation, a study has been undertaken during the past several weeks by Drs. Bryan S. Finkle, James C. Garriott, Institute of Forensic Sciences, Dallas, Richard F. Shaw, San Diego County Coroner's Office and Yale Caplan, State of Maryland Medical Examiner's Office, Baltimore. The study included seven site visits and a telephone survey of six additional Medical Examiner-coroner offices covering some major metropolitan areas and states across the United States. The general purpose of these activities was to assess propoxyphene in the forensic toxicology of drug fatalities but specifically to:

1. Evaluate the accuracy of the data on DPX deaths in Dr. Sidney Wolfe's letter to HEW Secretary Califano dated Nov. 21, 1978.

2. Critique the method and cases which are reported to the DAWN data collection system.

3. Consider how (2) differs from the Finkle-McCloskey system of case evaluation.

4. Determine if Heroin is responsible for more deaths than propoxyphene.

5. What other drugs, particularly analgesics, outweigh Heroin in this context.

The following summarizes the findings:

A. Telephone Survey

(i) PHILADELPHIA (City and County)

In 1974 this site had $14.0/10^6$ population DPX associated cases, i.e. 28 cases. Cases peaked to a maximum in 1975 and have since decreased steadily: 1975-38, 1976-25, 1977-25, 1978 $<$20.

Propoxyphene - DPX
Tricyclic Antidepressants - TADS

DPX ranks sixth in frequency of occurrence in toxicology cases, behind alcohol, carbon monoxide, narcotics, tricyclic antidepressants and barbiturates. The greatest current increase is in TAD's, flurazepam and cocaine.

DPX continues to occur principally in multiple drug intoxications.

(ii) OAKLAND - ALAMEDA County

In 1974 there were 11 DPX associated cases, at $10.0/10^6$ population.

There has been little change in the past 4 years with 7-10 cases per year.

Opiate narcotic deaths have decreased; and greatest increase in TAD cases.

(iii) ORANGE COUNTY - California

In 1974 experienced 15 DPX associated cases at $10.0/10^6$ population. Since then cases have remained relatively constant each year at about 15-20 per year.

The drug still ranks in the top five in frequency of occurrence, usually in multiple drug deaths. No information available on narcotics deaths, but TAD, flurazepam, diazepam increasing and a surprising reappearance of chloral hydrate.

(iv) N. CAROLINA STATE

There were 32 DPX cases in 1974 at $6.4/10^6$ population. The cases reached a peak in 1975 at 50 cases and have since decreased steadily, 1976-34, 1977-36, 1978-32. This experience is best summarized in a report to the Southern Medical Journal, V. 70, No. 8:938, Aug. 1977 by Page Hudson, et al.

There is evidence of an "improving situation" re DPX. Opiate narcotics have never been a major fatality problem in this state at less than 15 cases/year during the past eight years.

There has been a major increase in amitriptyline cases. The character of the DPX cases, i.e., multiple drugs, accidental and suicide cases remains unchanged since 1975.

(v) STATE OF MARYLAND

This site was not included in the 1975 Finkle study. However, cases reached a maximum in 1975 as the following table shows:

	1974	1975	1976	1977	1978
PROPOXYPHENE	19	45	32	43	<40
OPIATE NARCOTICS	-	54	44	17	-
BARBITURATES	-	42	39	43	-
TOTAL DRUG DEATHS	-	118	103	140	-

There has been a significant decrease in Heroin deaths, whereas propoxyphene associated cases have decreased only slightly. DPX's role remains essentially in multiple drug fatalities.

B. SAN DIEGO SITE VISIT

(i) The geographical area and population base used for the DAWN reporting system and the 1975 Finkle study are the same at this site.

(ii) The population has increased; 1975 - 1.4, 1977 - 1.6, 1978 - 1.7×10^6. Wolfe's population base is accurate but it is important to note that the DPX cases per million population on P. 12 of his letter is for a 3 year period which obviously inflates the DPX case frequency. The rate per year matches closely the Finkle study (BF: 92 cases 1974-77 = $57.8/10^6/3$ YR = 19.3/YR. SW: 95 cases 1974-77 = $59.8/10^6/3$ YR = 19.9/YR)

(iii) At this site the DPX involved cases which are reported to DAWN and those included in a Finkle type study are the same because no "Drug Related" cases are reported to DAWN on the 1977 OMB 43-R-0545 form. This is because there is considerable danger of misinterpretation of these cases. (Drug Related cases have been reported since November 1978). A "Drug Related" case does not necessarily mean that the drug was in any way contributory to the death; e.g., in deaths from Gun Shot Wounds, Motor Vehicle Accidents, a paraplegic who might die from non-drug related causes. The case merely indicates that DPX or its metabolites were present in the blood or tissues at any concentration.

The Finkle case criteria and DAWN "Drug Induced" cases match much more closely, but even here there is a problem for DAWN because most of the DPX cases involve multiple drugs and the

separate agents are not reported in a way that permits discrimination of their potency or relative toxicological significance in a given case. In consequence, cases in which, for example, a combination of alcohol and barbiturates was the cause of death, but in which also toxicologically insignificant concentrations of DPX were detected, would be reported as "Drug Induced" and recorded by DAWN and Wolfe as a "DPX case". It was not possible in the time available to inspect and evaluate each of these actual cases but it certainly should be done if a true picture of DPX toxicology is to be clearly established. It should be noted that the Finkle study was a SURVEY and that local pathologists' opinion relative to the role of DPX as expressed on the case death certificates was not questioned. There is obviously room for a more critical evaluation of these "Drug Induced" and "Drug Related" cases which probably reflect unrealistically high numbers.

(iv) At San Diego, DPX continues to occur principally in multiple drug deaths. Section B of the DAWN report form does NOT indicate a rank ordering of potency.

	(July-Dec.) 1973	1974	1975	1976	1977	1978
DPX Total	17	23	19	26	24	17
DPX Only	8	6	3	6	3	2
DPX & Alcohol Only	2	0	6	1	6	2
DPX in Multiple Drug Cases	7	17	10	19	15	13

(v) Deaths from Heroin are decreasing rapidly; this probably reflects the current strength of the street drug which is 3-5% Heroin in contrast to 20-25% in the early 1970's. The ratio for DPX-to-Heroin associated deaths is extremely variable for any particular period of time and is, therefore, an unreliable indicator of increased DPX fatalities.

e.g. FIRST 6 MONTHS 1977

12 DPX CASES
28 HEROIN CASES
RATIO 1 : 1.2

FIRST 6 MONTHS 1978

	HEROIN	DPX
ACCIDENT	17	7
SUICIDE	0	1
UNDETERMINED	0	2
	17	10

RATIO 1 : 1.7

DPX is almost constant since 1975 whereas Heroin has decreased - the ratio then quite erroneously indicates an apparent increase in DPX cases.

There are NOT more DPX deaths in San Diego (even currently) than Heroin fatalities. By selection of site and time, and use of the DPX/ Heroin ratio, it is possible to show that DPX is a major problem compared to Heroin, but it is quite misleading and a futile exercise in assessing the toxicity of propoxyphene (cf DALLAS).

(vi) DPX does rank as a drug frequently encountered in forensic toxicology. For 1977 the ranking (detected in blood and tissues by analysis) is:

1. Alcohol 490
2. Barbiturates 86
3. Morphine (Heroin) 83
4. Tricyclic Antidepressants 46 (Amitriptyline 36, Imipramine 4, Desipramine 6)
5. Propoxyphene 31
6. Diazepam 31
7. Codeine 17
8. Doxepin 13

The TADS, codeine, Doxepin,PCP, and Chloral Hydrate are all increasing significantly each year. DPX is not. Comparing two analgesics: Codeine occurs at about half the frequency of DPX, but is increasing. This does raise the question, if DPX were to be removed, what would fill the void. Today codeine and acetaminophen are the likely toxicological candidates.

DALLAS CITY AND COUNTY SITE VISIT

The geographical area and population served by this site is not the same as the DAWN reporting area, but it does represent the major portion of the DAWN area and the Medical Examiner's office does make DAWN reports. [M. Examiner 1.3, DAWN 1.7×10^6].

All of the criticisms of the DAWN reporting system especially the lack of discrimination between cases, and in toxic significance, noted at the San Diego site were also found in Dallas. This site does report "Drug Related" cases which undoubtedly explains the larger case numbers seen in the Wolfe letter versus those in the 1975 Finkle survey.

Propoxyphene associated cases peaked in 1975 and are now stable, or even decreasing slightly, as follows:

	1972	1973	1974	1975	1976	1977	1978
DPX Only	2	5	5	4	7	9	3
MULTIPLE DRUGS	11	5	11	22	6	11	13
TOTAL	13	10	16	26	13	20	16

The Suicide, Accident Manner of Death has not changed since the Finkle study.

There are more DPX associated deaths than Heroin at this site, since 1975.

In the first half of 1977: 8 DPX (4 DPX only and 4 Multi-drug) against 1 Heroin death.

In 1978: 11 intravenous narcotism cases (9 morphine and 2 Dilaudid) 16 DPX.

Drug Frequency Pattern is as follows:

	TOTAL DPX	HEROIN	TAD-		BARBS		ALCOHOL
			ALONE	MIXED	ALONE	MIXED	ACUTE
1972	13	28	3	-	10	32	-
1973	10	11	4	1	8	9	6
1974	16	9	3	1	9	13	11
1975	26	5	-	5	8	28	5
1976	13	14	4	6	4	11	16
1977	20	4	7	9	7	10	10
1978	16	9	2	20	2	13	-

The mixed drug cases are the most critical toxicologically. e.g.

1974	22 of 125 cases
1975	50 of 128 cases
1976	21 of 117 cases
1977	22 of 115 cases

All of the other observations and comments from this site match San Diego very closely. Particularly, DPX is a multi-drug case problem which is NOT revealed in DAWN, or the significance of DPX in multi-drug cases.

PHOENIX-MARICOPA COUNTY SITE VISIT

The jurisdictional population of the Medical Examiner's office is 1.2 million. This site reports to the DAWN system, but only "Drug Induced" cases; not those classified as "Drug Related".

The current experience with DPX cases is as follows:

	From July 1973	1974	1975	1976	1977	1978
TOTAL DPX	8	18	28	10	16	15
DPX ONLY	3	2	6	4	5	5
DPX & Alcohol Only	1	8	10	3	3	2
DPX IN MULTIPLE DRUG CASES	4	8	12	3	8	8

Propoxyphene is the most frequently detected drug in postmortem cases, followed by morphine, barbiturates and TAD's. The frequency of other analgesics such as acetaminophen and codeine is of a very low order.

DPX has only outranked morphine (Heroin) for the past two years because, although DPX has itself decreased, Heroin deaths have dramatically dropped to negligible numbers:

	1973	1974	1975	1976	1977	1978
(Heroin)Morphine Cases	13	31	41	33	5	6

MIAMI - DADE COUNTY SITE VISIT

The forensic toxicology experience with propoxyphene and Heroin is as follows:

Year	Total Toxicity Cases	Heroin(Morphine)	Propoxyphene Total	Propoxyphene Multiple Drug	Propoxyphene Suicides	Propoxyphene Acciden
1973	174	11	11	5	11	0
1974	228	14	10	3	7	3
1975	261	30	12	9	7	5
1976	245	24	6	5	5	1
1977	252	9	11	5	11	0
1978	249	22	11	8	9	2

It should be noted that at this site Heroin fatalities still out number propoxyphene associated cases. There has been no significant decrease in narcotic deaths which is contrary to the general U.S. experience since 1976. DPX is principally a multiple drug case problem in a population dominated by suicides.

DETROIT - WAYNE COUNTY SITE VISIT

The jurisdictional population at this site is 2.7 million, and matches the DAWN reporting area.

All sections of the DAWN, Medical Examiner report form are completed routinely. DAWN case numbers are greater than those in the Finkle study because only cases in which DPX was significant were included in the latter whereas DAWN records all cases in which the drug was detected.

The following table gives the relevant case data:

	1974	1975	1976	1977	1978
Total Toxic Cases	3539	3289	3371	2747	3116
Total Drug Cases	--	423	287	151	123
Total DPX Cases	24	32	17	14	16
DPX Alone	6	8	7	6	6
DPX & Alcohol Only	4	6	3	2	0
DPX in Multiple Drug Cases	14	19	7	6	10

The DPX case numbers are decreasing and the main involvement is in multiple drug deaths. Suicides are predominant. This office is very conservative in designating a death as suicide, preferring "Not determinable" if there is any doubt at all.

	1974	1975	1976	1977	1978
Total DPX Cases	24	32	17	14	16
Suicides	8	13	4	7	10
Accidents	1	2	1	0	1
Undeterminable	15	18	11	7	5

Until 1975 Detroit has a national lead for the annual number of Heroin deaths. Those deaths have dropped largely since 1976 but still outnumber DPX involved cases by a wide margin.

HEROIN (MORPHINE)

1971	-	1973	1974	1975	1976	1977	1978
100	→	250	→ 300	341	208	66	55

Here, the toxicologist believes that federal law enforcement and control over Mexican heroin has severely restricted availability, and this is the main reason for the case decrease, rather than the weaker strength of the current street heroin.

In frequency of occurrence DPX is fourth behind alcohol, diazepam and morphine, and is followed immediately by the barbiturates.

Other analgesics, codeine, acetaminophen and meperidine are of a very low frequency.

BRYAN S. FINKLE, PH.D.
DIRECTOR, CENTER FOR HUMAN TOXICOLOGY

Dr. Bryan S. Finkle is Director of the Center For Human Toxicology at the University of Utah Health Sciences Center, and holds Assistant Professorships in Pharmacology-toxicology and Pathology. He was born and educated in England, and spent ten years in forensic science at the Scotland Yard laboratory, specializing in toxicology. An 18-month leave of absence was spent in the U.S. in 1963-65, first as a research associate in toxicology at Cuyahoga County Coroner's Office and Western Reserve University School of Medicine, and then as a criminalist specializing in toxicology in the Santa Clara County Laboratory, California. He joined the latter permanently in 1966, and lectured in forensic toxicology at the University of California School of Criminology at Berkeley in 1971.

Dr. Finkle is consultant to several government and private agencies involved with the toxicology of drug abuse. He is Past President of the International Association of Forensic Toxicologists, Past President of the Forensic Sciences Foundation, Past Vice-President of the American Academy of Forensic Sciences, and a member of several state, national, and international organizations of forensic scientists and toxicologists.

For the past 20 years he has been closely associated with research into the problems of alcohol and drugs. His main professional interests are in the study of operations management in toxicology; instrumental, automated analytical methods; GC-MS as a tool in toxicology; and studies and experiments to provide a data base for interpretation of analytical toxicology data. He has made many contributions to the scientific literature and books concerned with forensic and clinical toxicology.

CURRICULUM VITAE

BRYAN S. FINKLE

BIRTH: Sunderland, England, March 5, 1936.

ADDRESS: Center For Human Toxicology, University of Utah, Salt Lake City, Utah 84112, Telephone (801) 581-5117.

EDUCATION:

National Certificate: Chemistry, Physics, Pure Mathematics, Rutherford College of Advanced Technology, Durham University, England, 1956.

Higher National Certificate: Chemistry, Physics, Pure Mathematics, Northampton College of Advanced Technology, London University, England, 1957.

Forensic Science Training Program, specializing in Toxicology, Metropolitan Police Forensic Science Laboratory, New Scotland Yard, London, England. Directed by L.C. Nickolls, 1956-60.

Ph.D., Department of Pharmacology, University of Utah College of Medicine, 1977.

PROFESSIONAL CERTIFICATIONS:

American Board of Forensic Toxicology.

Forensic Alcohol Supervisor, Certified by California State Department of Public Health.

Forensic Blood Alcohol Analyst, Certified by the California Association of Criminalists.

EMPLOYMENT:

Primary Academic Appointment. Assistant Professor of Biochemical Pharmacology and Toxicology, College of Pharmacy, University of Utah, 1977 -

Assistant Professor of Pathology, College of Medicine, University of Utah, 1978 -

Director, Center For Human Toxicology, University of Utah, Salt Lake City, Utah, January 1976 -

Head, Divisions of Analytical, Clinical and Forensic Toxicology. Center For Human Toxicology, University of Utah, Salt Lake City, Utah 1973-75.

Chief Forensic Toxicologist. Laboratory of Criminalistics, Department of District Attorney, Santa Clara County, California, 1966-73.

Research Associate and Demonstrator in Toxicology. Western Reserve University, Cleveland, Ohio, 1963-64.

Research Associate, Toxicology. Cuyahoga County Coroner's Office, Cleveland, Ohio, 1963-64.

EMPLOYMENT CONTINUED:

Forensic Scientist (Toxicology). Metropolitan Police Forensic Science Laboratory, New Scotland Yard, England, 1956-63, 1965.

Analytical Chemist. Swan-Hunter, Newcastle-on-Tyne, England, 1953-56.

UNIVERSITY OF UTAH COMMITTEE APPOINTMENTS:

College of Pharmacy Space Committee 1977 -

University Instrumentation Committee 1978 -

TEACHING EXPERIENCE:

Lectures and Demonstrations in Toxicology, Western Reserve University School of Medicine, Department of Pathology, Cleveland, Ohio, 1963-64.

Orientation and In-Service Training in Toxicology, Laboratory of Criminalistics Professional Staff, Department of District Attorney, Santa Clara County, California, 1966-74.

Lecturer in Alcohol, Drugs and Driving, Attorney Staff, Department of District Attorney, Santa Clara County, San Jose, California, 1966-73.

Lecturer in Analytical Toxicology, Resident Pathologists, Valley Medical Center, Santa Clara County, California, 1964-65.

Lecturer in Alcohol, Drugs and Driving Problems, Santa Clara County School Districts, California, 1969-71.

Lecturer in Toxicology, School of Criminology, University of California at Berkeley, 1971.

Leader, Seminar Workshop in Clinical Toxicology, American Society of Medical Technologists, Las Vegas, Nevada, 1971.

Lecturer, Drug Education Course for Teachers and Counselors, "Dialogue on Drugs", University of California, Santa Cruz Extension, 1971.

Lecturer, Advanced Analytical Toxicology, University of Sao Paulo, Brazil, Department of Toxicology and Biopharmaceutical Sciences, Sao, Paulo, Brazil,1973-;

Lecturer, Advanced Clinical Toxicology, American Society of Clinical Pathologists, Chicago, Illinois, 1974 -

Leader, Seminar Workshop, Analytical Techniques in Clinical Toxicology, Intermountain States American Society of Medical Technologists, Wyoming, 1976.

University of Utah: Principles of Pharmacology, College of Medicine.
Graduate Course in Analytical Toxicology, Col. of Pharmacy.
Clinical Toxicology, School of Medical Technology and College of Nursing.
Drug Abuse, College of Pharmacy
Analytical Techniques in Pharmacology, Col. of Medicine
Clinical and Forensic Toxicology, Col. of Medicine.

DOCTORAL GRADUATE STUDENT TRAINING:

Postdoctoral Fellows: Kevin L. McCloskey 1976-78
Michael Morgan 1979-80

Preliminary Examinations Committee 1978, James Melby

Thesis Committee, Toxicology of Cocaine, 1977-79. Ronald Jordon.

Prethesis Research Rotations 1978-79: Leslie Bornheim, Donna Webber.

RESEARCH GRANTS AND CONTRACTS AWARDED:

A National Assessment of Drug Involvement in Postmortem Cases. #271-76-3327. Awarded July 1, 1976-77. National Institute on Drug Abuse.

The Forensic Toxicology of Propoxyphene, 1975 - Eli Lilly Pharmaceutical Company.

Pharmacokinetic Service Laboratory for the Quantification of LAAM and Other Drugs by Gas Chromatography-Mass Spectrometry. #271-76-3323. Awarded May 1, 1976 - National Institute on Drug Abuse.

Toxicological Analysis in Cases of Suspected Sudden Infant Death Syndrome. #240-76-0052. Awarded June 30, 1976-78 Health Services Administration: Office for Maternal and Child Health.

Forensic Toxicology and Pharmacokinetics of Drugs in Drivers. #271-76-3323. Awarded Sept. 29, 1977 - National Institute on Drug Abuse.

The Forensic Toxicology of Diazepam, 1976-78 Hoffmann-La Roche, Inc.

Toxicology of Glutethimide and Other Nonbarbiturate Sedative Hypnotic Drugs. U.S.V. Laboratories 1977 -

Incidence of Drugs Among Fatally Injured Drivers, (Subcontractor) DOT-NHTSA. Awarded Oct. 1, 1978 -

Cannabinoids: Survey of Drug Related Casualties. #271-78-3532. NIDA Awarded Sept. 1978 -

PROFESSIONAL SOCIETIES:

American Academy of Forensic Sciences
American Association for the Advancement of Science
American Association of Clinical Chemists
California Association of Criminalists (1965-76)
California Association of Toxicologists
Forensic Science Society of Great Britain
International Association of Forensic Toxicologists
Sigma Xi
Western Pharmacology Society
Society of Toxicology

HONORS:

Distinguished Service Award, Santa Clara County District Attorney's Office, California, 1965.

American Academy of Forensic Sciences Award of Merit, 1974, for Outstanding Service to Forensic Science. (Fellow and Past Vice-President)

President. International Association of Forensic Toxicologists, 1975-78.

President. Forensic Science Foundation 1976-78.

Certificate of Honor, Awarded for Research in Toxicology by University of Ghent, Belgium, 1976.

Visiting Professor of Toxicology, University of Sao Paulo, Dept. of Toxicology and Biopharmaceutical Sciences, Sao Paulo, Brazil, 1973, 1978.

Honorary Member. Gesellschaft Fur Gerichtliche Medizin. German Democratic Republic 1978.

PROFESSIONAL AREAS OF SPECIAL INTEREST:

Staff and Laboratory Operations Management in Toxicology.

Instrumental, Automated Methods in Analytical Toxicology.

Gas Chromatography-Mass Spectrometry as an Analytical Technique in Toxicology, Pharmacology and Clinical Medicine.

Studies and Experiments to Provide Data Base for Interpretation of Analytical Toxicology Results.

Biodisposition of Drugs and Metabolites in Man.

PROFESSIONAL CONSULTATION ACTIVITIES:

Fluoride Toxicity Studies, Union Carbide, Cleveland, Ohio 1964.

GC/MS Applications in Forensic Science, Hewlett-Packard, 1969-70.

Development of Analytical Systems and Forensic Science Education Program, NASA Space Technology Applications, Jet Propulsion Laboratory, Pasadena, California, 1969-75.

GC/MS Applications Development in Forensic Sciences and Biomedicine, Finnigan Corporation, Sunnyvale, California, 1971-77.

Toxicology Methods for Drugs of Abuse, Veterans Administration Hospitals, Palo Alto, California, 1971-73. Salt Lake City, Utah, 1973 -

Quality Control and Proficiency Testing in Analytical Toxicology; Toxicology Resource Committee, College of American Pathologists, 1974 -

Toxicology Research and Evaluation, National Institute on Drug Abuse Review Com. Washington, DC, 1974 -

Gas Chromatography-Mass Spectrometry. National Institute on Drug Abuse 1974 -

PROFESSIONAL CONSULTATION ACTIVITIES CONTINUED:

Determination of Marijuana in Drivers, Midwest Research Institute and Department of Transportation, Kansas City, Missouri, 1974-75.

Forensic Toxicology and Medico-legal Investigation, State of Montana, 1974-

Bioavailability Studies, CIBA Pharmaceutical Company, Summit, New Jersey, 1974-75.

Medico-legal Aspects of Propoxyphene, Eli Lilly Pharmaceutical Company, 1975-

Medico-legal Aspects of Diazepam. Hoffmann-La Roche Pharmaceutical Company, 1976

Toxicology of Glutethimide and Other Nonbarbiturate Sedative Hypnotic Drugs, U.S.V. Laboratories 1977-

Forensic Toxicology and Medico-legal Investigation, State of Wyoming 1977-

Quality Control and Proficiency in Analytical Toxicology, Center For Disease Control, Atlanta, Georgia 1977-

State of California, Dept. of Justice, Forensic Science Laboratory Drugs and Driving Program 1977-78.

National Institute of Law Enforcement and Criminal Justice, Forensic Toxicology 1977-

State of Utah, Forensic Science Systems Development 1978-

Province of Alberta, Canada. Forensic Toxicology Laboratory, Design and Operations Management, 1979.

PROFESSIONAL ORGANIZATION APPOINTMENTS:

Co-chairman and Secretary, California Association of Toxicologists, 1968-73.

Toxicology Editor, "What's New", American Academy of Forensic Sciences, 1968-70.

Toxicology Consultant, Forensic Science Foundation--Study of an Early Warning System of Drug Toxicity and Developing Patterns of Drug Abuse, 1971.

Toxicologist, Technical Advisory Committee, Santa Clara County Task Force, Drug Abuse Coordination Program, 1971.

Program Chairman, Toxicology Section, American Academy of Forensic Sciences, 1971-72.

Member, Santa Clara County Medical Society, Committee on Drug Abuse, 1971-73.

Vice-President, Santa Clara County Drug Abuse Coordinating Council, Pathway, 1972.

Secretary, Toxicology Section, American Academy of Forensic Sciences, 1973.

Program Chairman for American Academy of Forensic Sciences, 1973.

PROFESSIONAL ORGANIZATION APPOINTMENTS CONTINUED:

Chairman of the Council, American Academy of Forensic Sciences, 1973-74.

Chairman of the Toxicology Section, American Academy of Forensic Sciences, 1973-75.

National Safety Council, Executive Board, Committee on Alcohol and Other Drugs, 1973 -

Vice-President, American Academy of Forensic Sciences, 1973-74.

President, Executive Board, California Association of Toxicologists, 1973.

Member, Forensic Science Foundation, 1973-76.

Trustee, Board of Trustees, Forensic Science Foundation, 1975-76.

President, Forensic Sciences Foundation, 1976-78.

Member, Education Committee, American Academy of Forensic Sciences, 1974-75.

Representative for the American Academy of Forensic Sciences to the American Association for the Advancement of Sciences, Pharmaceutical Sciences Section, 1975-77.

Chairman, Ad hoc Committee on Toxicology Methods, American Academy of Forensic Sciences, 1974-76.

President, International Association of Forensic Toxicologists, 1975-78.

Regional Secretary General and Chairman, Toxicology Section; The International Association of Forensic Sciences, 1975-78.

PUBLICATIONS BOARDS - APPOINTMENTS:

Editorial Board, Journal of Forensic Sciences, 1975-

Editorial Board, Journal of Analytical Toxicology 1976-

Advisory Board Member, Handbook of Analytical Toxicology, Chemical Rubber Company. 1975-78.

Die Toxikologisch-Chemische Analyse, Editorial Advisory Board. Pub. Verlag Theodor Steinkopff.

Evaluation of Analytical Methods in Biological Systems. Editorial Advisory Board. Pub. Elsevier.

Editorial Consultant to Mosby Publishing Company.

Reviewer For: Clinical Chemistry
Analytical Chemistry
Science

INVITED PRESENTATIONS AND ABSTRACTS* AT SCIENTIFIC AND PROFESSIONAL MEETINGS:

* Gas Chromatography in Clinical Chemistry. Ohio Association of Clinical Chemists, Annual Meeting, Columbus, Ohio, 1964.

* Gas Chromatographic Identification of Central Nervous Depressants. National Association of Clinical Chemists, Boston, Massachusetts, 1964.

Applications of Gas Chromatography in Clinical and Forensic Toxicology. Northern California Association of Clinical Chemists, San Francisco, California, 1964.

* Quantitative Determination and Distribution of Meprobamate and Glutethimide in Biological Material. American Academy of Forensic Sciences, Toxicology Section, Honolulu, Hawaii, 1966.

* Drug Involvement in Drinking Driver Cases. California Association of Criminalists Seminar, 1967.

Leader/Chairman, Toxicology Workshop: Interpretation of Barbiturate Metabolite Methodology. California Association of Criminalists Seminar, 1967.

Leader/Chairman, Toxicology Workshop: Toxicology of Phenothiazine Drugs, California Association of Toxicologists, 1971.

* Computerization of Toxicological Data. California Association of Criminalists Semi-Annual Seminar, Tahoe, California, 1968.

M.D.A.: A Fatal Case. California Association of Criminalists, Semi-Annual Seminar, Los Angeles, California, 1969.

* "Now is the Winter of Our Discontent....": A Toxicologist's Introspective View of Pathology and His Role in Postmortem Investigation. American Academy of Forensic Science, Joint Session, Pathology, Biology and Toxicology, Chicago, Illinois, 1970.

* Examination of Marihuana Smoke for Cannabinoid Compounds. California Association of Criminalists Seminar, 1967.

Panelist, The Characteristics of a Center For Criminalistics Information California Association of Criminalists, Fall Seminar, Concord, California, 1970.

* GC/MS: Determination of Commonly Encountered Drugs in Body Fluid Extracts, The Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland, Ohio, 1971.

* GLC/MS As A Tool in Analytical Toxicology. American Association of Clinical Chemists, Northridge, 1971.

Seminar Leader, Modern Analytical Toxicology Problems. Southern Association of Forensic Scientists, Savannah, Georgia, 1971.

GLC/MS: State of the Art. American Association of Clinical Chemists, Buffalo, New York, 1971.

INVITED PRESENTATIONS AND ABSTRACTS* AT SCIENTIFIC AND PROFESSIONAL MTGS. CONT'D:

* Secobarbital Abuse and Traffic Accidents. Forensic Science Institute Seminar, Oakland, California, 1971.

Seminar Leader, Analytical Toxicology Problems Related to Drugs of Abuse. Unviersity of Indiana Medical School, Department of Pharmacology, Indianapolis, 1971.

* Laboratory Resources, Drugs of Abuse Analysis. Palo Alto Medical Clinic, Symposium on Practical Management of Drug Abuse Problems, Palo Alto, California, 1972.

* Applications of Computerized GC/MS in Forensic Toxicology. The Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy. Cleveland, Ohio, 1972.

* GC/MS: A Solution to Some Analytical Toxicological Problems. DuPont Symposium on GC/MS Applications. Wilmington, Delaware, 1972.

* Drugs of Abuse: Laboratory Resources. Western Conference on Criminal and Civil Problems. Wichita, Kansas, 1972.

Workshop Leader, Toxicology and Gas Chromatography. Denver, Colorado, 1972.

* Identification of Drug Metabolites by GC/MS and Computer Library Search Techniques. Society of Applied Spectroscopy, San Francisco, California, 1972.

Forensic Toxicology: Drugs and Their Effects. California Trial Lawyers Association, 1972.

Toxicology Workshop. California Society of Pathologists, 1972.

Analytical Problems Posed by Drug Abuse. Bay Area Seminar for Analytical Development, 1973.

* Physiological and Toxicology Aspects of Smoke Produced During Combustion of Polymeric Materials. Flammability Research Center, Univ. of Utah, 1973.

* New Observations on Narcotics Metabolism: Heroin and Cocaine in Blood and Urine. Brain Research Institute, University of Tennesee, 1973.

* New Analytical Methods in Forensic and Clinical Toxicology (Session President). American Academy of Forensic Sciences, Dallas, Texas, 1974.

* The Toxicology of Drug Abuse in California. Forum Brasileiro de Toxicologia. Instituto Oscar Freire, Sao Paulo, Brazil, 1973.

* Applications of Mass-Spectrometry in Forensic Toxicology. Second Latin American Congress in Toxicology, Santa Fe, Argentina, 1973.

INVITED PRESENTATIONS AND ABSTRACTS* AT SCIENTIFIC AND PROFESSIONAL MTGS. CONT'D.

Forensic Toxicology for Pathologists. College of American Pathology, Albuquerque, New Mexico, 1973.

* Indistinguishable from Magic--The Threat and the Promise of Laboratory Utopia. American Academy of Forensic Sciences, Dallas, Texas, 1974.

* Mass Spectrometry. Department of Pharmacology, University of Texas Medical School, San Antinio, Texas, 1974.

Education in Forensic Toxicology. Western Conference on Civil and Criminal Problems, Wichita, Kansas, 1974.

* Analytical Methods in Drug Metabolism. Department of Pharmacology, University of Indiana Medical School, Indianapolis, Indiana, 1974.

* Analytical Methods in Clinical and Forensic Toxicology. Eli Lilly Seminar Series. Indianapolis, Indiana, 1974.

* Instrumentation in Clinical Toxicology. American Chemical Society and American Association of Clinical Chemists. University of New Mexico, Albuquerque, New Mexico, 1974.

* GC/MS Computer Techniques. American Society of Clinical Pathologists, Chicago, Illinois, 1974.

* Interpretation of Clinical and Forensic Toxicology Data. American Chemical Society Seminar. Pharmacology Department, University of Vermont Medical School, Burlington, Vermont, 1974.

Forensic Science in State Law Enforcement. Attorney General's Conference Montana, 1976.

* Analytical Techniques Necessary to Detect the Drugged Driver. 6th International Conference on Alcohol, Drugs, and Traffic Safety, Toronto, Canada, 1974.

* The Use of a GC-MS-COM System of Analysis to Control Illegal Drug Use in Sport. 10th International Symposium on Chromatography, Advancement of Spectroscopic and Physico-Chemical Analytical Techniques. Barcelona, Spain, 1974.

Application of Isolated Perfused Liver to Toxicology Problems. California Association of Toxicologists, San Jose, California, 1974.

* GC/MS: Married Bliss or Breach of Promise? Seventh International Meeting of Forensic Sciences. Zurich, Switzerland, 1975.

* Traffic Safety as it Relates to Drug Abuse. The Citizen's Conference on State Legislatures, Snowmass, Colorado, 1975.

* GC-MS-Computer Techniques For The Identification of Poisons. Institute For Legal Medicine. Karl Marx University, Leipzig, G.D.R. 1975.

* Forensic Science in the United States. Medical-Legal Institute, Brno, Czechoslovakia, 1975.

INVITED PRESENTATIONS AND ABSTRACTS* AT SCIENTIFIC AND PROFESSIONAL MTGS. CON'D:

* Drug Detection in Drivers and Sportsmen. Institute for Forensic Toxicology. Charles University, Prague, Czech. 1975.

* The Use of Gas Chromatography-Mass Spectrometry in Clinical Toxicology. Indiana Clinical Biochemistry Forum, Indianapolis, Indiana, 1975.

The Center for Human Toxicology, Concept and Scientific Program. State of Illinois, Public Health-Toxicology Seminars. Chicago, Illinois, 1975.

* Forensic Toxicology Associated with Sudden Infant Death Syndrome. HEW Conference on SIDS. Santa Fe, New Mexico, 1975.

The Metabolism of l-alpha Acetyl Methadol. Department of Pharmacology, University of Indiana, School of Medicine, Indianapolis, Indiana, 1975.

* Isolated Perfused Liver Techniques Applied to Drug Metabolism and Toxicology Problems. American Academy of Forensic Sciences, Washington, D.C., 1976.

* The Forensic Toxicology of Propoxyphene. University of California at Davis, Dept. of Environmental Toxicology, 1976.

* GC-MS Development in Forensic Science. American Society of Mass Spectrometry, San Diego, California, 1976.

* GC-CI-MS Multiple Ion Monitoring Quantitative Analysis of l-α-Acetyl Methadol (LAAM) in Biological Samples. American Society of Mass Spectrometry, San Diego, California, 1976.

New Concepts and Developments in Toxicology Education and Research. The International Association of Forensic Toxicologists European Centennial Meeting. Ghent, Belgium, 1976.

Clinical Toxicology in Smaller Hospitals: Intermountain States Regional Medical Technology Seminar-Workshop. Wyoming, 1976.

* GC-MS in Biochemical Toxicology. University of Wisconsin at Madison, Dept. of Toxicology - Seminar Series. 1976.

* The Toxicology of Sudden Infant Death Syndrome. Second Annual SIDS Seminar. Providence, Rhode Island, May 1977.

* The Pharmacokinetics of LAAM. ICI-USA, Inc., Wilmington, Delaware, April 1977.

* Review of GC-MS in Forensic Toxicology. Mid-Atlantic and Northeastern Associations of Forensic Scientists. Mount Laurel, New Jersey, April 1977.

INVITED PRESENTATIONS AND ABSTRACTS* AT SCIENTIFIC AND PROFESSIONAL MTGS. CONT'D.

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SOUTHWESTERN
INSTITUTE OF FORENSIC SCIENCES
AT DALLAS
5230 Medical Center Drive
Dallas, Texas 75235

TELEPHONE 638-1131
AREA CODE 214
REPLY TO:
P.O. BOX 35728

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Office of the Medical Examiner

January 18, 1979

Sidney M. Wolfe, M.D.
Health Research Group
2000 P Street, N.W.
Washington, D.C. 20036

Dear Dr. Wolfe:

I am in receipt of your letter of December 18, 1978, concerning the Health Research Group's petition to the DEA, requesting transfer of propoxyphene to Schedule II of the Controlled Substances Act.

It is my opinion that the danger of propoxyphene is overinflated. Propoxyphene, like any other drug, can kill if misused. Accidental deaths from the use of propoxyphene are rare. Most alleged accidental deaths are drug abuse deaths. Any drug abused is dangerous.

More common than drug abuse deaths with propoxyphene are suicides. I do not think that by making propoxyphene difficult to obtain, one will decrease the rate of suicide. One will just change the drug or means used. All one has to do is to compare the method of suicide in different areas of the country to realize that access to drugs would make little difference in the suicide rate. In the latest data from our office, propoxyphene accounts for nine deaths; six of these were determined to be due to suicidal ingestion.

Along with your letter was a copy of a letter to Joseph Califano, Secretary of HEW. This was apparently a public letter, released on Tuesday, November 21, 1978. I think your cause might be taken more seriously if in this letter you had not included date which is incorrect. On Page 3, Table 2, you list the "DPX-related deaths" from 7/73 to 12/77. I am afraid that I cannot believe any of the figures in that Table. The reason I don't is that for Dallas you indicate that there were eighty such deaths in that time period. I would like to inform you that from January 1, 1973 to December 1977, in Dallas, there was a total of only thirty deaths due to propoxyphene. An additional twenty-five individuals, dying of a combination of multiple drugs, also had propoxyphene detected in their blood. If you include both, then the maximum number of cases would be sixty-five, rather than eighty. In fact, in a number of the "mixed drug deaths", the propoxyphene was present only in small therapeutic amounts and was only incidental.

Part of the "epidemic" of propoxyphene deaths being reported is that until fairly recently, many toxicology labs were deficient in their ability to detect propoxyphene. Therefore, such deaths were being missed for many years. Some of such cases, in which the propoxyphene was taken intravenously, were considered morphine deaths.

I am afraid that I also doubt your contention in Page 2 of your letter to Mr. Califano that propoxyphene was associated with more deaths than heroin-morphine in the first half of 1977. While methods of detection of propoxyphene are now readily available and used by toxicology labs, many of these labs are unable to detect morphine in the blood, thus they will miss rapid deaths from either morphine or heroin injections. If so, and some propoxyphene is found, it is possible that they may attribute such deaths to propoxyphene, rather than to morphine.

Thank you.

Sincerely yours,

Vincent J.M. DiMaio, M.D.

VJMD/aw

cc/Joseph Califano

APPENDIX

STATEMENT OF HON. JOSEPH A. CALIFANO, JR., SECRETARY OF HEALTH, EDUCATION, AND WELFARE

I am announcing today several actions to alert the public to the risks associated with Darvon, and to consider what further steps HEW should take to protect the public.

Darvon—a pain reliever which is also sold under other trade names such as Darvon Compound and Darvocet-N, and under its scientific name, propoxyphene—is the third most frequently described brand name drug in this nation. Last year, 31 million outpatient prescriptions were written for propoxyphene products. Propoxyphene is generally not dangerous when taken as directed; yet it is known to be a dangerous drug in a number of circumstances.

Propoxyphene is now second to barbiturates as the prescription drug most often associated with suicides.

Propoxyphene has also been a cause of accidental deaths, usually when used along with alcohol or tranquilizers.

Propoxyphene is also an addictive drug, though less so than heroin or morphine, and it is often abused.

For all these reasons—suicides, accidental deaths, and potential for addiction—propoxyphene is a drug which has raised serious concerns.

In November 21, 1978, the Health Research Group petitioned me to declare propoxyphene an imminent hazard to health under the Food, Drug, and Cosmetic Act, and to remove the drug immediately from the market. Alternatively, they asked me to recommend to the Attorney General that propoxyphene be shifted from Schedule IV to Schedule II of the Controlled Substances Act, an action which would restrict production and sale of the drug in various ways.

On the basis of the limited evidence now available, I do not believe that there is sufficient justification for the extraordinary step of declaring propoxyphene an imminent hazard and immediately removing it from the market without the opportunity for a hearing.

Accordingly, I am denying the Health Research Group's petition at this time.

However, the current evidence is sufficient to conclude that propoxyphene should be prescribed and taken only with extreme care:

(*a*) Doctors and dentists should not prescribe Darvon or other forms of propoxyphene to people who may be suicidal or addiction prone.

(*b*) Doctors and dentists should warn patients that Darvon and other forms of propoxyphene can be lethal if taken to excess, or if taken along with alcohol of tranquilizers.

(*c*) Pharmacists should be cautious in filling prescriptions for Darvon and other forms of propoxyphene where there is reason to suspect abuse, or where the patient is taking other drugs which may present risks when combined with this drug. Pharmacists should also warn people orally and on prescription labels not to take the drug with alcohol or tranquilizers.

(d) People who do choose to take propoxyphene should be careful not to take it with alcohol or tranquilizers.

These are precautions which health professionals and the public can take on their own to limit the risks from propoxyphene. Although I believe the current evidence does not warrant a finding of imminent hazard at this time, I also believe that this evidence compels us to inform the public promptly of the risks involved. and to evaluate further the dangers of propoxyphene.

Therefore, based on the recommendations of FDA Commissioner Donald Kennedy and of the Surgeon General, Dr. Julius Richmond, I am today directing the Commissioner of the Food and Drug Administration (FDA) and the Surgeon General to take the following actions:

First, within 30 days, to distribute to one million doctors, dentists, pharmacists and other health professionals throughout the country a special Drug Bulletin which will warn of the risks of taking propoxyphene, and urge them to talk with patients about these risks. FDA will also disseminate information on propoxyphene to the public, by means of an article in the FDA Consumer magazine, and through public service announcements in the media.

Second, on April 6, to hold a hearing to allow the public an opportunity to comment on the need for additional FDA regulatory action on propoxyphene, including withdrawing it from the market. The hearing will consider the ways

in which propoxyphene is used, its effectiveness, and its risks. In addition, the FDA will conduct a comprehensive study of the scientific data of propoxyphene, including the evidence and testimony taken recently by Senator Gaylord Nelson's Senate subcommittee.

While I am denying the imminent hazard petition at this time, I have directed Commissioner Kennedy to notify me immediately if, at any time during the course of the public hearings and study of the data, evidence develops which may warrant the declaration of an imminent hazard.

Third, by June 1, to complete the administrative process, including deliberations by an advisory committee, and prepare a recommendation to the Justice Department on whether propoxyphene should be placed under more stringent controls as provided in the Controlled Substances Act. Propoxyphene is currently subject to Schedule IV, which places no limits on production, allows prescriptions to be filled merely by a telephone call by the doctor to the druggist, and permits up to five refills every six months. The Health Research Group has proposed that propoxyphene be transferred to Schedule II, which would place limits on the manufacture of the drug, prohibit dispensing it without a written prescription, and ban refills.

Rather than summarily suspending propoxyphene from the market, I have directed that steps be taken both to protect the public immediately from the health risks, and to conduct a more deliberate, comprehensive review of the facts concerning the drug. In the course of this review, I have asked the FDA actively to solicit the participation in the hearing of doctors, coroners, researchers, and others who have information on propoxyphene.

In the case of propxyphene, these are still unresolved questions which prevent us from saying at this time that it constitutes an imminent hazard to health. But as we take the steps I have announced today, we will develop better answers to these questions, and we will consider whether propoxyphene should be removed from the market as an imminent hazard, whether its removal should be considered in the ordinary administrative process, whether more stringent controls should be placed on its production and sale, and whether the warnings on the labels should be strengthened.

One unresolved question is how extensive is the harm associated with Darvon and other forms of propoxyphene. In 1977, there were 607 propoxyphene-related deaths reported to the Drug Enforcement Administration's Drug Abuse Warning Network (DAWN), which covers about one-third of the United States. This was more deaths than for any other prescription drug, and that fact alone is obviously a cause for concern. However, under the DAWN reporting system, mentions of propoxyphene as related to death can mean merely that the deceased person had the drug in his or her blood, not necessarily that it was in fact the cause of death.

Another unresolved question is the extent to which deaths that are associated with propoxyphene are accidental, result from abuse, or are sucides.

Yet another unresolved question concerning propoxyphene is whether or not it is effective—whether it has any benefits which justify its use despite the risks which exist. Propoxyphene has been a very widely used pain reliever. Propoxyphene is occasionally sold alone, and it may have some therapeutic advantages for people who react adversely to other pain relievers. But it is far more often sold as a compound with pain relievers such as aspirin or acetaminophen. Several studies indicate that most or all of the effectiveness of these combinations is due to the elements other than propoxyphene. Nevertheless, since pain is such a subjective symptom, some people may experience, psychologically or physically, more relief from propoxyphene which is prescribed by a doctor than they would from over-the-counter pain relievers such as aspirin. Overall, the best evidence thus far is that propoxyphene is no more effective—and may be less effective—than aspirin, codeine, and other pain relievers.

Because of these unresolved questions concerning propoxyphene and the uncertainties in the data, I have asked the Commissioner of the FDA to focus on these questions as well as others:

1. What amount of propoxyphene alone is required to produce fatalities? What is the relationship of this amount to the proper dosage? Does propoxyphene build up in the body?

2. Do deaths result when propoxyphene is taken at recommended doses, either alone or in combination with other drugs? How many of the deaths associated with propoxyphene are suicides; how many are accidents resulting from abuse; and how many are accidents resulting from normal use?

3. How does propoxyphene cause death? Is it primarily by depressing respiration, or is there a previously unrecognized toxic effect on the heart?

4. Is there scientific evidence that propoxyphene adds significantly to the effectiveness of aspirin or other pain relievers in combination products?

The public hearing and FDA study will seek the best answers we can develop to these questions. Meanwhile, as the result of the actions I have announced today, the doctors and people of this country will be warned that propoxyphene should be taken only with care.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

In re Petition to Suspend New Drug Applications for Propoxyphene

OFFICE OF THE SECRETARY

I. Issue

The issue presented to me is whether, as currently labeled and distributed, propoxyphene, a drug for use in the relief of pain, should be declared an "imminent hazard" under section 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), and approval of the new drug applications for the drug summarily suspended prior to the initiation of the ordinary procedures for withdrawal of approval of those applications. Thus, I must decide whether there is now sufficient evidence available showing that the continued use of propoxyphene constitutes so serious a threat to public health as to warrant an interim suspension of general distribution of the drug pending initiation and completion of the procedures to determine whether propoxyphene should be removed permanently from the general market.

This proceeding was initiated by a petition filed by the Health Research Group (HRG), a consumer advocacy group concerned with health matters. HRG also petitioned the Department of Justice to impose new restrictions on the production and dispensing of propoxyphene under the Controlled Substances Act, 21 U.S.C. 801. In its petition to me, HRG requests that, in the event I do not suspend marketing of the drug, I support the HRG petition at the Department of Justice.

II. Background

Propoxyphene hydrochloride, alone or in combination with aspirin, phenacetin, and caffeine, was first approved and marketed in 1957. The most widely sold brand names of propoxyphene products are Darvon, Darvon Compound. and Darvon Compound-65, all manufactured by Eli Lilly and Company.

The original approval of propoxyphene was on the basis of safety only. After the enactment of the Drug Amendments of 1962, the efficacy of propoxyphene products was reviewed by the National Academy of Sciences/National Research Council, which concluded that the products are effective for the relief of pain. In the early 1970's, the Food and Drug Administration approved as safe and effective additional products manufactured by Eli Lilly and Company containing propoxyphene: the napsylate salt of propoxyphene either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA). All propoxyphene products are "new drugs" and are subject to new drug application (NDA) requirements.

In 1977, through joint activity by the Department of Health, Education, and Welfare and the Department of Justice, all products containing propoxyphene were controlled under Schedule IV of the Controlled Substances Act for the first time, because of their potential for abuse. This action limited refills on propoxyphene prescriptions, and imposed certain labeling and recordkeeping requirements on manufacturers. In 1978, FDA revised the labeling of these products to contain additional warnings on adverse reactions, particularly adverse interactions of propoxyphene with alcohol, tranquilizers, sedative-hypnotics, and other central nervous system depressants; and to advise on management of propoxyphene overdoses.

III. History of this Petition

On November 21, 1978, Sidney M. Wolfe, M.D., Director of HRG, petitioned me to take one of two actions:

(*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 avail-

able only as an investigational drug for treating narcotics addicts or, in the alternative,

(*b*) "Support [the Health Research Group's] petition . . . [to the Attorney General and the Administrator of the Drug Enforcement Administration] to reschedule [propoxyphene] as a Schedule II narcotic which would impose production quotas and prohibit refills of prescriptions."

Dr. Wolfe argues that propoxyphene is relatively ineffective: "[a]t present the preponderance of properly-controlled studies fail[s] to show that DPX [propoxyphene] 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." HRG also contends that propoxyphene is unsafe because its limited effectiveness is outweighed by the several hundred deaths per year that are associated with its use. These deaths are reported in the Drug Enforcement Administration's Drug Abuse Warning Network (DAWN). HRG suggests that many of these deaths are the result of accidents rather than suicide.

Upon receiving the HRG petition, I requested FDA Commissioner Donald Kennedy and his scientific colleagues in the Bureau of Drugs to evaluate it and advise me on the proper response. On January 17, 1979, Commissioner Kennedy forwarded to me the Bureau's detailed analysis of the use and risks of propoxyphene, accompanied by a discussion of the options available to me and copies of the materials cited in the analysis. Additional materials were compiled by the Bureau and submitted to me on February 10, 1979.

On January 30, February 1, and February 5, 1979, the Senate Select Committee on Small Business held hearings on the safety and effectiveness of propoxyphene. The testimony presented at those hearings has been included in the materials submitted to me.

In addition to the materials referred to herein, I have relied on an examination of the full record created with FDA's assistance.

IV. Procedures and criteria for suspension of a new drug application

A. The Statutory Framework

The Secretary of Health, Education, and Welfare, and his delegate, the Commissioner of Food and Drugs, are responsible for the administration of the Food, Drug, and Cosmetic Act (the "Act"). 21 U.S.C. 301; 21 CFR 5.1. The provisions of the Act require that all "new drugs" be subject to a new drug application "approved" by the Secretary before they may be shipped in interstate commerce. 21 U.S.C. 505(a). To obtain approval for an NDA, a manufacturer must prove, *inter alia*, that such a drug is safe and effective.

The burden of establishing safety and efficacy of a new drug under the conditions prescribed, recommended, or suggested in the proposed labeling of the drug remains at all times on the manufacturer. Whenever new evidence warrants the conclusion that an approved new drug is unsafe or ineffective, the Food and Drug Administration is required to remove the drug from the market. Section 505(e) of the Act establishes two procedures for removing an approved drug from the market: "withdrawal" and "suspension."

1. Procedures for withdrawal of approval of an NDA.—The Act requires the Commissioner to withdraw an NDA if new evidence shows either that a drug is "unsafe for use" under the conditions for which it was approved, or that the manufacturer can no longer sustain its burden of demonstrating that the drug is safe and effective. The administrative procedure for withdrawing approval of an NDA ordinarily includes notice to the manufacturer of an opportunity for a hearing, the conduct of a full evidentiary hearing before a hearing officer, and a decision by the Commissioner based on the hearing record.

This procedure usually requires at least six months, and sometimes much longer. A drug may remain on the market for years while withdrawal proceedings are underway.

2. Procedures for suspension of approval of an NDA.—The elaborate procedural protections against improvident withdrawals emphasize the importance of the immediate suspension provision available under section 505(e) of the Act.[1] Established in 1962, this summary procedure permits the Secretary

[1] Section 505(e) provides, in pertinent part, as follows: If the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, hemay suspend the approval of such [new drug] application immediately and give the applicant the opportunity for an expedited hearing under this subsection. * * *

to act promptly to suspend approval of an NDA temporarily, and thereby remove the drug from the market, if it represents an "imminent hazard" to the public health. Once having suspended approval, the Secretary must provide the manufacturer with an expedited hearing on whether the drug should be permanently removed from the market. This special authority is vested solely in the Secretary, and may not be delegated.

The summary suspension procedure provides a critical procedural tool to carry out the obligation of this Department and of FDA to protect the public health and safety. Rapid action may be necessary if scientific data raise serious new questions concerning the safety of the drug. If new evidence or further and more careful analysis of existing evidence indicates that a life-threatening or other serious risk is present, the summary suspension procedure allows the Secretary to end promptly this serious risk. The summary procedure does not eliminate the need to conduct a full administrative proceeding to arrive at a final and conclusive judgment as to whether the drug should be permanently removed from the market.

B. Criteria for Suspension

In my 1977 order suspending the NDA's for phenformin under the "imminent hazard" provisions of the Act, I examined at length the text of section 505(e), the legislative history of the suspension provision, and pertinent court decisions. In re New Drug Applications for Phenformin, Order of the Secretary Suspending Approval, pp. 24–35 (DHEW July 15, 1977). I there concluded that the following factors should be weighed in determining whether approval of a new drug application should be suspended on the ground that continued use of the drug will constitute an imminent hazard to the public health:

1. The severity of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drug from the general market.
2. The likelihood that the drug will cause such harm to users while the administrative process is being completed.
3. The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the market, taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.
4. The likelihood that, after the customary administrative process is completed, the drug will be withdrawn from the general market.
5. The availability of other approaches to protect the public health.

These criteria were reviewed and upheld in *Forsham* v. *Califano*, 442 F. Supp. 203 (D.D.C. 1977).

V. Evaluation of propoxyphene under the criteria for suspension

In analyzing the record in this matter, I have been guided by the expert advice and opinions provided by FDA. In assessing and weighing the evidence, I have recognized that the record of a full evidentiary hearing is not before me.

Under the criteria set forth in part IV above, I am not persuaded that suspension of the propoxyphene NDA's should be ordered at this time. Although I am trouble by the evidence that propoxyphene carries life-threatening risks and is of limited efficacy, I believe that the standards for summary removal of a drug from the market have not been met by the evidence now before me. Therefore, I am denying for the present the HRG petition to declare propoxyphene an imminent hazard.

Nevertheless, because of my concerns about propoxyphene-associated deaths, I have ordered that several steps be taken to minimize as rapidly as possible avoidable harm from the drug and to gather further information on its risks and benefits.

I have directed the Commissioner to have FDA complete expeditiously a comprehensive review of all available information concerning propoxyphene to determine whether the various products containing the drug meet the safety and efficacy requirements of the Act and, thus, whether proceedings should be begun to withdraw the new drug applications for any or all of those products. In the course of this review, FDA will hold a public hearing to receive information and views on the continued marketing of propoxyphene. This hearing is scheduled for April 6, 1979. If at any time during this review evidence appears suggesting that

propoxyphene meets the criteria for suspension, FDA will immediately submit it to me. I will then consider, in light of that evidence, whether to suspend any or all of the NDA's for propoxyphene products.

Three other steps, described below, will provide information to physicians, dentists, pharmacists, and the general public, in order to increase awareness of the risks of propoxyphene, and may result in the imposition of additional restrictions on the production and distribution of the drug under the Controlled Substances Act.

A. Severity and Likelihood of Harm to the Public Health

The principal harm from propoxyphene is death. As HRG points out, propoxyphene is associated with a significant number of deaths. In 1977, the DAWN system reported 607 propoxyphene related deaths, more than those associated with any other prescription drug.

The DAWN data provide, however, only a very rough basis for estimating the true number of deaths that may be caused by use of propoxyphene. The DAWN reports include all deaths in which propoxyphene is found in the bloodstream of the deceased. In some of these cases, propoxyphene, particularly in conjunction with alcohol or a tranquilizer, may have caused the death. On the other hand, if propoxyphene happened to be found in the blood of a person who died in an unrelated car accident, that case would be reported in the DAWN statistics as a propoxyphene-associated death. The DAWN statistics also do not reflect all of the deaths in the country, but include only deaths in 24 major cities, covering slightly over 30% of the total U.S. population. Thus, it is likely that additional deaths associated with propoxyphene are occurring in areas which are outside the DAWN reporting system.

The absolute number of deaths must be viewed in perspective with the actual consumption of the drug. Propoxyphene is very widely used; last year, about 31 million out-patient prescriptions were filled, and additional quantities of propoxyphene were used in hospitals, clinics, and physicians' offices. The ratio of propoxyphene-associated deaths (i.e., the number of times the drug is mentioned in coroners' reports included within the DAWN system) to dispensed out-patient prescriptions is lower than that for the barbiturates, the non-barbiturate sedative-hypnotics, amitriptyline, doxepin, and pentazocine. In fact, propoxyphene now ranks 12th out of 27 drugs in ratio of drug-associated deaths to dispensed prescriptions.

The reason for these deaths has long been thought to be suicide. Undoubtedly this motivation accounts for a significant proportion of the deaths. In its petition, HRG contends, however, that many of the deaths are the unintended result of drug abuse. The petition appears to suggest that in a search for euphoria, or because of a dependence on the drug, a user may take an excessive dose of propoxyphene or combine the drug with alcohol, narcotics, tranquilizers, sedative-hypnotics, or other substances that depress the central nervous system. The result can be an accidental death.

It is true that most identified propoxyphene-associated deaths appear to be the result of misuse of the drug, either in attempting suicide or in a drug abuse accident. In the report by Baselt *et. al.* (ref. 1), some of the cases classed as "accidental" involved such large quantities of propoxyphene that it is very likely that the drug was not being used for therapeutic purposes at the recommended dosage level.

Since filing the HRG petition, Dr. Wolfe has raised the question whether many of the deaths attributed to propoxyphene are due to a cariotoxic effect of its major metabolite, norpropoxyphene. This hypothesis, which would imply the existence of previously unidentified cases of propoxyphene-caused deaths possibly occurring at therapeutic doses of the drug, deserves serious consideration during FDA's review of the drug. At present, however, there is little evidence that this mechanism is a common factor in the deaths associated with propoxyphene.

Indeed, there is no clear evidence to date demonstrating that the therapeutic use of propoxyphene, in the absence of tranquilizers or alcohol, has caused accidental death. For example, although about one-third of the prescriptions for products containing propoxyphene are written for patients over age 60, these same patients experience only 8% of the deaths reported to be associated with propoxyphene. The largest incidence of deaths associated with propoxyphene products occurs among those in the 20–40 age range, who only receive about one-

third of the prescriptions, but experience roughly half the deaths. If propoxyphene-associated deaths were predominantly accidental, one would expect a much higher proportion of the deaths to occur among users over 60, assuming that older users are at least as likely to have fatal accidents as younger users.

The only serious health risk from propoxyphene other than the deaths described above is that the drug can cause physical dependence. Otherwise, it does not cause significant adverse reactions in many cases. Miller and Greenblatt (ref. 3 found that adverse reactions in hospitalized patients are infrequent and mild. Moreover, although the adverse reactions from propoxyphene that did occur were qualitatively similar to those from codeine and other analgesics used in the hospital setting, they occurred less frequently. Standard tolerance studies in volunteers revealed no significant difference between propoxyphene and placebo. In contrast, Goodman and Gilman (ref. 4 state that in equianalgesic doses, propoxyphene and codeine may be expected to produce similar incidences of side effects.

Thus, the principal harm posed by propoxyphene, and the basis of the HRG petition, are the deaths associated with the use of the drug in suicide attempts or accidental overdosing or interactions with other nervous system depressants in drug abuse situations.

B. Possible Harm From Immediate Suspension of Propoxyphene From the General Market

The principal harm from immediate suspension of a drug is the loss to patients of the benefit of its therapeutic effectiveness. Therefore, to assess the harm from suspension of propoxyphene, it is necessary to evaluate the available information concerning its effectiveness.

I recognize that the efficacy of analgesics is particularly difficult to assess. Pain is a subjective symptom. I am informed that although it can be quantitatively measured for purposes of clinical trials, the conduct of such trials is complicated by the fact that any analgesic will have a large placebo effect, typically in the range of 30–35% of the patients. In addition, many experts believe that in the case of prescription analgesics, such as propoxyphene, the placebo effect associated with the drug is increased by the facts that the drug is prescribed by a physician after consultation with the patient, that the capsules and tablets are colored rather than white, and that the drug is dispensed by a pharmacist.

Moreover, the overwhelming majority of prescriptions for products containing propoxyphene are for compounds containing it in combination with another analgesic, such as aspirin or acetaminophen. These combinations are clearly effective because of these other analgesics, and propoxyphene may make an additional contribution to their efficacy.

The literature on the efficacy of propoxyphene itself is mixed. HRG gives major attention to a literature review conducted by Miller *et al.* in 1970 (ref. 5). Miller cited 9 of 18 placebo controlled trials in which propoxyphene was found to be more effective than the placebo. Miller concluded that "[p]ropoxyphene 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." HRG also cites three subsequent studies that found no significant difference between propoxyphene and placebo. On the other hand, a 1978 study by Sunshine *et al.* (ref. 6) found propoxyphene napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was slightly better than a placebo. The usual dose (100 mg) was not tested. In a second review of the literature in 1977, Miller (ref. 7) reported that three studies showed that propoxyphene is no more effective than a placebo and that five studies showed that it is as effective as (but not more effective than) a standard analgesic.

For purposes of this preliminary assessment of propoxyphene's efficacy in reaching an imminent hazard determination, I conclude that propoxyphene has some, but limited, efficacy.

Thus, it is possible that there may be some risk to patients who do not adequately respond to (or, in relatively few cases cannot safely take) aspirin, acetaminophen, or other analgesics, and who would be deprived of propoxyphene. Moreover, propoxyphene does induce some degree of physical dependence, so that suddent unavailability could lead to withdrawal symptoms for some patients.

Other patients who depend particularly on propoxyphene for relief from pain may experience some suffering as the result of the abrupt removal of the drug from the market. For these people, the most likely substitute for propoxyphene is codeine, which is widely believed to be even more addictive than propoxyphene. If presented with the sudden disappearance of propoxyphene from the market, physicians would still be reluctant to prescribe codeine for more than intermittent use, and patients would be reluctant to take it.

C. Likelihood of Final Action to Withdraw the Drug from the General Market[2]

The Bureau of Drugs in FDA has responsibility for initiating a withdrawal proceeding (21 CFR 314.200), but has not proposed that the NDA's for propoxyphene be withdrawn. Possible grounds for withdrawal of these NDA's include (1) that evidence from clinical experience shows the drug to be unsafe, (2) that new evidence not available when the NDA's were approved, together with the original evidence supporting the approvals, demonstrates that the drug is no longer shown to be safe, and (3) that the new evidence, evaluated together with the evidence in the original NDA's, supports a finding that there is a lack of substantial evidence that the drug is effective. 21 U.S.C. 355(e) (1), (2), and (3).

The issues concerning the safety and effectiveness of propoxyphene are difficult and complex.

Although the drug is associated with a large number of deaths, many of these deaths appear to be related to misuse of the drug rather than its use in accordance with the labeling directions. It is not clear that many of these deaths—those related to suicide attempts—would be prevented if propoxyphene were immediately removed from the market.

In addition, the record currently does not contain sufficient evidence for me to make a finding of imminent hazard based on two as yet unresolved issues raised by HRG's petition:

(*1*) The extent to which propoxyphene is dangerous, if at all, when used in accordance with the labeling;

(*2*) The extent to which labeling restrictions are effective in controlling use of propoxyphene that may lead to death.[3]

On the basis of the information with respect to propoxyphene available to me at this time, I cannot conclude whether or not one or more of the new drug applications is likely to be withdrawn. That determination cannot be made until the issues concerning the efficacy and safety of propoxyphene in light of all the data now available have been developed more fully.

D. Potenial Alternative Means To Prevent Hazard

During the period FDA is evaluating further the safety and efficacy of propoxyphene, three steps can be taken to protect the public health. I am concerned by the various dangers posed by propoxyphene; use in suicides, accidental deaths from the interaction of the drug with alcohol or other drugs that act on the nervous system, and dependence on the drug. Therefore, I am directing that these problems be addressed immediately without awaiting the final FDA decision on whether propoxyphene meets the statutory standards of safety and effectiveness. I believe that implementation of the following actions will reduce the hazards to the public health.

First, the Department will promptly evaluate HRG's proposal to transfer propoxyphene from Schedule IV to Schedule II of the Controlled Substances Act. If this transfer were made, the production of propoxyphene would be limited by government-determined quotas; all distribution of the drug would be on special order forms; and prescriptions for the drug would not be refillable and would have to be in writing (i.e., telephone prescriptions would be prohibited). The Assistant

[2] Because final responsibility for deciding whether the new drug applications for propoxyphene should be withdrawn is delegated to the Commissioner of Food and Drugs, I have not asked Dr. Kennedy to comment on this matter, and he has reserved judgment until formal administrative procedures have developed a complete record for his review.

[3] In the phenformin case, the evidence did support a finding that phenformin was dangerous even if used in accordance with the labeling. In addition, the evidence showed that phenformin was being used widely outside of the indications set out in the labeling.

Secretary for Health, who has delegated authority to make drug scheduling recommendations on behalf of the Department, will make a recommendation to the Department of Justice on propoxyphene in the near future, after consideration by FDA and its Drug Abuse Advisory Committee.

Second, FDA will expeditiously prepare and distribute appropriate information for physicians, dentists, and pharmacists regarding the risks associated with the use of propoxyphene. This information will encourage physicians and dentists to reconsider the risks of and need for the drug in specific cases. It should also help deal with the problems of suicide and accidental deaths from drug interactions by making physicians and dentists more cautious in prescribing the drug for patients who may be suicidal or who may be using alcohol or other drugs affecting the central nervous system. This information will also encourage pharmacists, when dispensing propoxyphene, to put on the container warnings against taking the drug in combination with tranquilizers or alcohol.

Third, FDA will promptly prepare and distribute appropriate information for the general public, in the form of a published article or otherwise, regarding the risks associated with the use of propoxyphene.

Although I believe these actions will help protect the public, I do not believe that the completion and evaluation of these actions are necessary before a decision on the suspension or withdrawal of the propoxyphene NDA's can be made.

VI. Conclusion

At this time, I do not believe that there is sufficient evidence available showing that the continued use of propoxyphene constitutes so serious a threat to public health as to warrant the extraordinary action of summary suspension of general distribution of the drug, pending initiation and completion of the procedures to determine whether propoxyphene should be removed permanently from the general market. Based on the record currently before me, I am unable to declare propoxyphene an "imminent hazard."

The Act carefully balances the safeguards against improvident withdrawals of NDA's and the need to protect the public health from significant risks. The suspension power vested in the Secretary should be used sparingly, when it is likely that the drug will ultimately be withdrawn from the market and immediate action will prevent serious harm during the pendancy of the withdrawal proceedings. The issues in the case of propoxyphene are in significant doubt, and I am not prepared to predict their outcome at this time.

The fact that I am not granting the HRG petition at this time does not mean that further evidence cannot lead me to an opposite conclusion. If, in the course of FDA's further review of propoxyphene, new information is developed to show that propoxyphene meets the criteria for suspension, I will act promptly. Furthermore, the other steps that I have directed should reduce the risks that propoxyphene poses to the public health, while FDA holds its hearing to determine whether the drug should be removed from the market.

Dated February 15, 1979.

JOSEPH A. CALIFANO, Jr.,
Secretary of Health, Education, and Welfare.

[From the New York Times, Feb. 18, 1979]

A COMPANY AT WAR: HOW LILLY DEFENDED DARVON—MARSHALING FORCES IN "RED FLAG ALERT"

(By Peter T. Kilborn)

INDIANAPOLIS.—In 1957, scientists of Eli Lilly & Company here introduced a painkiller that was safer and less addictive than the morphine and codeine that most physicians were then prescribing. The generic name of the drug was propoxyphene hydrochloride, and the brand name, Darvon. In due course, it became the third most prescribed drug in the United States. Then, on Nov. 21, 1978, the media relations director at Lilly, Russell Durbin, received a call from an Associated Press reporter in Washington. What, he asked, had Lilly to say about a petition to ban Darvon?

Thus began a long and wrenching episode for the 103-year-old giant of the pharmaceutical industry. With insulin, the Salk antipolio vaccine in the mid-50's, and an ever-growing stable of antibiotics, Lilly has prided itself on doing

well for its stockholders by doing good for the sick. With what became a torrent of press calls, Lilly now found itself exposed to the scorching glare of public scrutiny, facing allegations that Darvon was on one hand even less effective than aspirin in killing pain and on the other, more common even than heroin in killing people.

Companies can be knocked to their knees in such confrontations: The Firestone Tire and Rubber Company was forced to recall its entire 500 line of radial tires last year in the face of compelling evidence that the tires were unsafe. But industry can also win now and then: Two years ago, the Food and Drug Administration ordered a ban of saccharin because it could cause cancer. Soft-drink companies, among others, argued that the risk was small in relation to the benefits of saccharin; they helped persuade Congress to order a moratorium that remains in effect.

Now here was Lilly, its brow to the barrel of a deadly serious adversary. The author of the petition was Dr. Sidney M. Wolfe, director of the Health Research Group in Washington, a low-budget but high-impact consumer interest organization sponsored by Ralph Nader. Management considered Dr. Wolfe's assertions flawed and distorted readings of statistics on drug abuse, as well as a blatant attack on the company's integrity.

Lilly's response to the Wolfe allegations illustrates how companies have to proceed when the debate over them and their products moves outside the comfortable forum of the Government agencies that regulate them. The company would deal more with the question of the hazards of Darvon, than with the older, less inflammatory charges comparing it with aspirin. It would argue the case on the merits, but would also have to keep an eye on public relations. And the Lilly defense would show how two sides in such a dispute can take essentially the same information to reach entirely different conclusions.

"*What petition?*" Mr. Durbin wondered as he fielded the reporter's call. But he got the gist of it, and he promised to get right back. He hurried from his office on the 10th floor of Lilly's meandering headquarters building to the serene, wood-layered 12th. Edgar G. Davis, vice president for corporate affairs, was standing outside his office, ending a phone call at his secretary's desk and trying to get off to a meeting.

The meeting would have to wait a moment now. "That was a red-flag alert," said Mr. Davis. He and Mr. Durbin reported the call to J. Richard Zapapas, group vice president. Mr. Zapapas in turn called Richard D. Wood, chairman and chief executive, who was out of the building attending a meeting of the Lilly Endowment, a foundation set up by heirs of the company founder, Col. Eli Lilly, who won his rank on the Union side in the Civil War. A committee that came to be called the Darvon Working Group would convene for the first time that afternoon, and Mr. Davis would be in charge.

The bulk of Lilly's work ended last week, with completion of reams of documents that make up the company's side of the case, and it has reason to be encouraged. Late last week, Joseph A. Califano Jr., Secretary of Health, Education and Welfare, denied Dr. Wolfe's call for a ban on Darvon. The debate, meanwhile, has shifted from the public arena, at least for now, into the F.D.A. and the Drug Enforcement Administration, where Lilly feels it belongs.

At best, however, Lilly won a draw. Mr. Califano didn't ban the drug, but he did order an intensive review that could lead to tighter restraints on its use. Darvon is still immensely profitable, and it accounted for $70 million of corporate revenues last year of $1.85 billion, putting Lilly near the top of the industry. But Darvon's heyday has passed. Sales fell to 1.17 billion pills and capsules last year from a peak of 1.57 billion in 1974, the result in part of studies showing that aspirin was often a better painkiller.

Lilly's experience in defending its product on a public battleground took an enormous toll. "It becomes a gigantic P.R. war with blunt instruments," said Mr. Wood, 52, an urbane, meticulous, rather remote presence in the otherwise collegial environs of the Lilly executive suite. "It's dumb," he said. "It's unfortunate. It's time-consuming. Doing this doesn't create anything. It's defensive."

The effort diverted a score of Lilly executives, full time, from their normal responsibilities: Lilly has been forced to allocate supplies of Mandol, a new antibiotic that was introduced in October, and Mr. Wood blamed the Darvon affair for stalling plans to expand production. Also delayed, he said, was the American debut of Cefaclor, an antibiotic that Lilly now sells only in Britain.

Meanwhile, John Holt, 53, secretary and general counsel of Lilly's pharmaceu-

tical division, was distracted from F.D.A. negotiations seeking to define the rules governing research on recombinant DNA, the outer limit of drug industry research. It could offer a means of obtaining insulin from human cells, a far better source than the pancreases of swine and cattle now being used. James M. Gorrel, director of Government programs, dealt only with Darvon for two months. "The only mail I looked at," he said, "were things that were hand-carried in here and I was told, 'This has something to do with Darvon.' "

Typists in Lilly's Word Processing Center worked 480 hours of overtime, cranking out the documents for the Darvon defense. Two computer analysts did the equivalent of four months' work in two, reviewing Darvon data that Lilly computers spent 289 hours compiling. Over a 10-week period, the Lilly corporate jet, which normally flies one round-trip between Indianapolis and Washington a week, made eight extra trips, and Covington & Burling, Lilly's Washington law firm, committed one partner full time to the project and another half time.

THE INDUSTRY'S NEMESIS

The man who went after Lilly is the pharmaceutical industry's No. 1 nemesis. Dr. Wolfe helped bring about the ban, three years ago, of Red Dye No. 2, widely used in food then but found to cause cancer, and of phenformin, an oral diabetic drug that was found to hurt more people than it helped. He is a graduate of Cornell and of the Western Reserve medical school and did his residency and internship at the National Institutes of Health. He is a vigorous 41-year-old who runs the 400-meter dash for the Potomac Valley Seniors Track Club.

"I've been aware for a long time that Darvon is not a very effective painkiller, and I never prescribed it to patients," said Dr. Wolfe. "Then I became aware of widespread abuse and of people dying from taking Darvon. I reviewed all the literature on Darvon-related deaths and concluded that more people were dying from Darvon than from any other drug."

Dr. Wolfe actually delivered two petitions that day, both prepared by Michael Lipsett, a young lawyer now in his third year of medical school in San Diego. One went to Mr. Califano asking that the F.D.A. declare propoxyphene an imminent hazard and ban it from the marketplace. If not that, Dr. Wolfe asked that the F.D.A. support the second petition, to the Justice Department and its Drug Enforcement Administration, urging that propoxyphene be reclassified to prohibit refills and over-the-phone prescriptions.

He then delivered copies to the Washington press corps and to Senator Gaylord Nelson, Democrat of Wisconsin, the drug companies' top political watchdog and chairman of the Senate Subcommittee on Monopoly and Anticompetitive Practices. "The object," said Dr. Wolfe, "was to get the question aired and to get people to ask what the F.D.A. was doing."

Mr. Davis, 47, had been planning to take off the week between Christmas and New Year's, when Lilly shuts down. He and his wife were to go to Florida to join their three children, now at colleges in New England. Mr. Holt was planning to be in Florida as well as Dr. Robert H. Furman, 60, vice president for corporate medical affairs, had scheduled a ski week in Aspen. Now they would all stay in Indianapolis. The Davis children would come to Indianapolis, and their father would see them on Christmas Day.

A STRATEGY SHAPES UP

Mr. Holt became Mr. Davis's executive officer on the working group. The 11 other members included Dr. Furman, Mr. Gorrel, Stephen A. Stitle, chief of the Washington office, William D. Cairns, director of public relations, Robert Luedke, director of market planning, and Charles E. Redman, director of scientific information services and one of Lilly's 450 Ph.D.'s.

A strategy began to fall into place. Said Mr. Wood: "My job was to say, O.K., here's the problem. Analyze what the petitions said. Make sure we have the proper people in the corporation paying attention to them. There's a psychology you have to put forward: We're on firm ground. We have to turn the charges around."

Right from the start, there were problems. CBS News called when Mr. Durbin was upstairs alerting Mr. Davis. A correspondent, Leslie Stahl, wanted to interview a Lilly executive in Washington. But Mr. Stitle, a 33-year-old lawyer, was in Indianapolis that day, so Lilly lost an early round in the public relations war—a chance to air its case on network television.

The Darvon Working Group would meet every Monday at 2 p.m. and every Tuesday at 10:30 a.m. It, in turn, would report to the Darvon Policy Group, composed of Mr. Wood, Dr. Earl B. Herr, president of Lilly Research Laboratories, Mr. Zapapas, Cornelius W. Patinga, an executive vice president, Eugene L. Step, president of the pharmaceutical division, C. Harvey Bradley Jr., the top corporate attorney, and Mr. Davis, who was the link between the two groups. The policy group, meeting every Tuesday at 8:30 a.m., would set straategy and deadlines for the working group.

In business school, such committees are called matrix organizations. Lilly management uses them to tackle temporary problems requiring expertise from several parts of the company. "The problem here is how do you reach out into the corporation and pull together the bits and pieces of information you need to make a solid case?" said Mr. Davis. "This was a major, unfounded threat, with implications for a product and the company," Mr. Davis said. "We knew we were right. And we knew we had to get the data to make that case."

Dr. Wolfe's fatality data, the working group found, were built in part on material gathered for the Drug Enforcement Administration through the Drug Abuse Warning Network, known as DAWN. It collects medical examiners' reports on drug-related fatalities in 23 metropolitan areas. Dr. Wolfe had shown that fatalities involving propoxyphene, of which 95 percent is Lilly's Darvon, had soared 25 percent in 1977 to 590. That put it second only to heroin with 751, and because the network covers only big cities, where heroin use is concentrated, Dr. Wolfe figured that Darvon deaths in smaller communities pushed the Darvon toll above heroin's. He also contended that most of the deaths resulted from accidental overdoses.

WHAT THE TAPES SHOWED

"Our task,' said Mr. Luedke, "was to get the DAWN data study," the material from which the D.E.A. compiled the statistics that Dr. Wolfe used. The source was IMS America Ltd., leading experts in pharmaceutical market research and a company that both the Government and the industry consider reliable.

Mr. Luedke asked IMS for the raw material, the 455,000 reports, recorded on 16-track computer tape, showing incidents of drug-related fatalities from 1974 through 1978. The tapes were then turned over to Dr. Redman, who, with a team of five analysts and statisticians, put them through the Lilly computer, updating them as Mr. Luedke obtained 1978 statistics in daily calls to IMS.

The tapes did not exonerate Lilly. They showed hundreds of deaths each year from overdoses of propoxyphene. But DAWN's reports showed only the results for all of 1977, not for each quarter, and Lilly made a happy discovery: "By looking at the tapes," said Mr. Luedke, "we found most of the mentions in the first quarter, and that they then began to drop." The fall of Darvon-related deaths continued from then on, to the end of 1978.

Lilly also went to Dr. Bryan S. Finkle, a toxicologist at the University of Utah, who, in an earlier study, had reported a rise in Darvon-related deaths in the early 1970's. Now he found a decline matching the Lilly analysis. He also found that most deaths resulted from massive overdoses, often in combination with alcohol or other drugs, indicating that many of the fatalities were probably suicides, not accidents. As for the heroin charge, Lilly found that in relation to the number of prescriptions filled, propoxyphene ranked way back in 11th place among all drugs as a cause of death.

Lilly then wanted to see if its own warnings of the hazards of misusing Darvon had had any impact on physicians. They asked IMS to poll them. The sampling of 514 physicians showed that 88 percent were aware of warnings against the abuses of Darvon and that 91 percent considered the drug safe when used as prescribed.

These developments broke in the days just before Christmas. Lilly had still not constructed an airtight case. It was clear that Darvon could at times be lethal with relatively small overdoses, as Dr. Wolfe charged, increasing the risk of accidental fatalities. And data from the IMS tapes still raised questions. Some medical examiners don't file reports on drug-related deaths as promptly as others, so some doubt about the downward trend for 1978 remained. But time was getting short. On Friday, Dec. 29, Lilly would have to answer Dr. Wolfe's petitions in a preliminary submission to the F.D.A. and the D.E.A.

The typists in the Word Processing Center began working right through the night then, cranking out the documents that the working group would assemble

into what came to be called the "Red Book." The company lawyer, Mr. Holt, marked the hours he worked those days in his pocket agenda. He logged 16 on one and 20 on another.

THE RED BOOKS DEPART

The Red Book, nearly an inch thick, was compiled and bound during the afternoon and evening the day before the deadline. At 12:40 A.M. Oec. 29, Mr. Holt took a box of 20 and left for the Indianapolis airport, and the books departed later that morning at 7 A.M. on an American Airlines flight to Washington. Mr. Stitle met the flight and then hurried around the capital, delivering 10 copies to the F.D.A., three to the D.E.A., and a couple to Covington & Burling.

By then, another shoe was falling. Mr. Stitle learned that Senator Nelson was likely to hold hearings on the Wolfe petitions. That would put the Darvon affair squarely before the public. Senator Nelson himself couldn't banish Darvon, but he could bring immense pressure on the regulators to do so, and he could certainly heat up the debate.

"Originally, we thought we would have to do an analysis for the regulatory agencies involved," said Mr. Davis. "Now we had to be sure that the complex scientific view of things was communicated and developed with recognition that the data would be examined by people who were not regulators."

And Dr. Furman added: "The Nelson hearings meant we would have to overprepare. We would have to conjure up dirty questions, false accusations, misinterpretations of things we have said."

The Darvon Working Group proceeded with its final submission to the regulators, this one a blue book nearly 2 inches thick, but now much of the group's attention was shifting to Washington. Mr. Stitle began working hours like Mr. Holt's. His 8-year-old son asked when daddy was coming home from vacation. Mr. Stitle didn't go on vacation but he never got home before 8-year-olds go to bed.

INVITATION TO THE HEARINGS

He and Mr. Davis, Dr. Furland and Raymond O. Clutter, assistant corporate secretary and general counsel, made a trip to see the Nelson staff to brief it on their view of Darvon.

"We've heard reports that you would look at this," Mr. Stitle recalled saying. "If you're going to have hearings, we want to appear." Mr. Stitle also visited other senators on the subcommittee. "These are the allegations," he told them. "These are Eli Lilly's view of the facts. Here's what Dr. Wolfe is saying. These are what we think the fallacies are."

Senator Nelson wrote to Mr. Davis on Jan. 15 formally inviting Lilly to testify at the hearings. They would be held on Jan. 31, Feb. 1 (a Wednesday and Thursday), and on Feb. 5 (a Monday). Dr. Furman, who won a top debating award while a student at Union College in Schenectady, would speak for the company, Lilly decided.

Dr. Wolfe would testify on the first day, but Lilly's turn wouldn't come until the third. That presented a problem: The press could be expected to cover the opening session, where it would report Dr. Wolfe's charges, but it would be six days before Lilly could present its side.

This time, Lilly was ready. On the day that Dr. Wolfe appeared, Lilly had news releases ready giving its side of the issue, and to assure the company similar exposure on the networks, Mr. Davis stood ready to be interviewed.

He made his debut on ABC, and moments later his secretary in Indianapolis received a call from a woman in Los Angeles who wanted to know if she could keep taking Darvon.

Nevertheless, the hearings were rough. It was clear even to Lilly that Darvon, after two decades on the market, was neither a fully effective nor entirely safe drug. "I would imagine that Darvon's days are probably numbered," observed Senator Lowell P. Weicker Jr., a Connecticut Republican and heir to the Squibb drug fortune, the panelist most sympathetic to Lilly's position.

"We ourselves" said Dr. Furman, "will probably come up with a better product."

Senator Gaylord Nelson at hearing he called on drug.

Presenting the Darvon side: From left, Dr. Robert H. Furman, John Holt and Edgar G. Davis, Eli Lilly & Company executives.

ELI LILLY & CO.

[In millions]

Year ended Dec. 31	Revenues	Net income	Earnings per share	Quarter ended	Revenues	Net income	Earnings per share	Dividend
1978 [1]	$1,852.1	$277.5	$3.81	December 1978 [1]	$474.4	$64.5	$0.89	$0.45
1977 [1]	1,550.2	223.5	3.07	September 1978	416.1	59.8	.85	.40
1976	1,397.8	202.7	2.87	June 1978	444.5	70.0	.99	.40
1975	1,267.2	184.0	2.66	March 1978	482.5	79.0	1.12	.40
1974	1,148.2	176.1	2.55	December 1977 [1]	391.6	52.9	.73	.355

Total assets, Dec. 31, 1977	$1,752,645,000
Current assets	1,203,294,000
Current liabilities	489,384,000
Stockholders equity	44,361,000
Stock price, Feb. 16, 1979 N.Y.S.E. consolidated close	51¾
Stock price, 52-week range	54–38⅜
Employees, Nov. 6, 1978	23,300

[1] Restated.

[From the New York Times, Feb. 18, 1979]

THE WORLD OF DARVON

Propoxyphene is a mild-to-moderate analgesic, or painkiller, that affects the central nervous system. The Darvon brand of propoxyphene sold by Eli Lilly & Company accounts for 95 percent of all propoxyphene sales in the United States and is available either as pure propoxyphene or mixed with other analgesics.

The other leading analgesics are acetaminophens, which are sold over the counter as Tylenol and Datril, and aspirin. Pharmacists fill about 18 million prescriptions for Darvon and Darvon compounds a year. It costs 10 to 20 times more than the over-the-counter analgesics.

The propoxyphene molecule, which Lilly discovered, is a close cousin of the methadone molecule. It is mildly addictive and can produce a euphoria.

No one fully understands the nature of pain, how analgesics subdue it or why one analgesic controls some types of pain better than another analgesic. Lilly has found that aspirin usually works better than propoxyphene in dealing with inflammation. And Dr. Charles G. Moertel of the Mayo Clinic in Rochester, Minn., has shown in tightly controlled studies than cancer patients realize more pain relief from both asprin, acetaminophens, and codeine than they do from propoxyphene. But in relieving many other pains, such as those of arthritis and tooth extractions, propoxyphene ahs been found highly effective.

One explanation for Darvon's effectiveness may be psychological. Because a doctor prescribes Darvon, patients may merely believe it works and, in a way, will it to work.

The bigger question concerning Darvon, however, is safety. Medical examiners in major cities have found traces of Darvon in the bodies of hundreds of persons believed to have died from drug overdoses.

Lilly and the Food and Drug Administration say that the drug is never fatal when taken in prescribed doses and when not mixed with other potent drugs or alcohol. And Dr. Bryan S. Finkle, a prominent toxicologist, has produced studies asserting that half the reported deaths are suicides.

However, Dr. Sidney M. Wolfe, who initiated the recent attack on Darvon, argues that the deaths are more likely accidental. His own studies contend that the body stores propoxyphene longer than most drugs and that a fatal dose can be accumulated unintentionally.

The F.D.A. will now explore those questions. The Secretary of Health, Education and Welfare, Joseph A. Califano Jr., has given the agency a June 1 deadline to decide whether to reclassify propoxyphene under the provisions of the Controlled Substances Act. Two years ago, Darvon was added to Schedule IV of the act, which allows physicians to telephone prescriptions to pharmacies and allows consumers up to five refills per prescription. Dr. Wolfe wants it put in Schedule II, which would prohibit both refills and telephone prescriptions.

DEPARTMENT OF DEFENSE,
ASSISTANT SECRETARY OF DEFENSE,
Washington, D.C., January 22, 1979.

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

DEAR MR. CHAIRMAN: In your letter to the Secretary of Defense dated January 8, 1979, you requested information on the usage and disposition of the drug Darvon and other preparations containing propoxyphene within the Department of Defense. We are unable to provide all of the data requested in questions 2 and 3. In instances where data are not provided, accounting records are not maintained individually by category of drug; therefore, the retrieval of requisite information is inordinately expensive and time consuming. If the committee believes the excluded data to be absolutely necessary for its hearings, we will make every effort to assemble the additional information. However, the following is provided pursuant to your request.

a. NSN 6505-00-890-2024 Propoxyphene Hydrochloride, Aspirin and Phenaglycodol Capsules (Darvon-Tran), 500s was standardized in December 1964, reclassified to terminal status in January 1971 and deleted in August 1974.

b. NSN 6505-00-913-7907 Propoxyphene Hydrochloride, Aspirin, Caffeine and Phenacetin Capsules (Darvon Compound-65), 100s was standardized in September 1965, reclassified to terminal status in March 1971 and deleted in June 1971.

c. NSN 6505-00-784-4976 Propoxyphene Hydrochloride, Aspirin, Caffeine and Phenacetin Capsules (Darvon Compound-65), 500s was standardized in January 1965, reclassified to terminal status in May 1971 and deleted in December 1971.

d. NSN 6505-00-958-2364 Propoxyphene Hydrochloride Capsules, USP, (Darvon), 65 mg, 500s was standardized in January 1965 and recommended for reclassification to terminal status in February 1971. However, this item was not deleted since two services recommended retention. 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, i.e. peptic ulcers.

e. Any commercially available analgesic may be and probably is being purchased and used instead of these deleted drug products. Enclosure (1) provides a listing of all oral analgesic tablets and capsules currently standardized which are possibly being used in place of the deleted items.

f. Though not specifically requested one other Propoxyphene containing analgesic was also deleted. NSN 6505-00-725-6992 Propoxyphene Hydrochloride Capsules, USP, (Darvon) 32 mg, 500s was standardized in January 1965, reclassified to terminal status in July 1970 and deleted in October 1974.

g. Enclosure (2) provides a list of all drug products containing Propoxyphene currently in the Federal Supply Catalog. These products are identified by NSN, generic name and trade name. Date of standardization is also noted.

h. The amount spent by DoD for preparations containing Propoxyphene for each year since fiscal year 1970 is not available. However, for fiscal year 1977 and fiscal year 1978 the amounts were $526,050 and $359,690 respectively.

i. The proportions of Defense drug procurements purchased centrally and locally by the individual services are not readily available. This information is normally reported only as total medical supplies purchased from standard stock and open (local) purchase; drug purchases are not normally reported separately. Only the Navy has actual figures available on drug purchases and these are limited. For 17 Naval Regional Medical Centers, during the July-September 1978 period, 75 percent of drug purchases were from standard stock and 25 percent were from open purchase. For the Army to obtain this data would require a special report and extensive effort for Army medical activities worldwide. From the purchases reported for all medical supplies, the Air Force was able to extrapolate the drug portion and estimates 84 percent of drug purchases were from standard stock and 16 percent were from open purchase.

I trust this information will satisfy your requirements.

Sincerely,

VERNON MCKENZIE,
Principal Deputy Assistant Secretary.

Enclosure.

ALTERNATIVE ANALGESIC TABLETS AND CAPSULES IN THE FEDERAL SUPPLY CATALOG

Generic name	Trade name	NSN
Acetaminophen and codeine phosphate capsules, 500's	Phenaphen No. 3	6505-01-041-2623
Acetaminophen and codeine phosphate tablets, 500's	Tylenol No. 3	6505-00-147-8347
Acetaminophen tablets, USP, 0.325 g, 50's	Tylenol	6505-01-017-1625
Acetaminophen tablets, USP, 0.325 g, 1,000's	Tylenol	6505-00-985-7301
Acetaminophen tablets, USP, 0.325 g, individually sealed, 250's	Tylenol	6505-00-117-7327
Aspirin, aluminum hydroxide gel, dried, and magnesium hydroxide Tablets, 500's.	Ascriptin	6505-00-135-2783
Aspirin, Caffeine, and phenacetin tablets, 1,000's	Empirin Compound	6505-00-100-6245
Aspirin tablets, USP, 325 mg, 36's		6505-01-016-2224
Aspirin tablets, USP, 0.324 g, 100's		6505-00-100-9985
Aspirin tablets, USP, 0.324 g, 1,000's, enteric coated	Ecotrin	6505-00-063-5631
Aspirin tablets, USP, 0.324 g, 1,000's		6505-00-153-8750
Aspirin tablets, USP, 0.324 g, individually sealed, 100's		6505-00-118-1948
Butalbital, aspirin, caffeine, and phenacetin tablets, 30's	Fiorinal	6505-00-117-8620
Butalbital, aspirin, caffeine, and phenacetin tablets, 1,000's	Fiorinal	6505-00-962-4375
Butalbital, aspirin, caffeine, and phenacetin tablets, individually sealed, 30's.	Fiorinal	6505-00-118-2129
Chlorzoxazone and acetaminophen tablets, 500's	Parafon Forte	6505-00-764-3313
Codeine phosphate and aspirin tablets, 1,000's	Ascodeen-30	6505-00-149-0116
Codeine phosphate and aspirin tablets, individually sealed, 25's	Ascodeen-30	6505-00-118-2347
Codeine sulfate tablets, NF, 30 mg, 100's		6505-00-118-2132
Codeine sulfate tablets, NF 30 mg, individually sealed, 25's		6505-00-056-8056
Ethoheptazine citrate and aspirin tablets, 1,000's	Zactirin	6505-00-687-7901
Ibuprofen tablets, 400 mg, 500's	Motrin	6505-00-128-8035
Indomethacin capsules, NF, 25 mg, 100's	Indocin	6505-00-926-2154
Indomethacin capsules, NF, 25 mg, 1,000's	Indocin	6505-00-931-0680
Indomethacin capsules, NF, 25 mg, individually sealed, 100's	Indocin	6505-00-118-2776
Meperidine hydrochloride tablets, USP, 50 mg, 100's	Demerol	6505-00-126-9375
Meperidine hydrochloride tablets, USP, 50 mg, individually sealed, 25's.	Demerol	6505-00-851-6589
Naproxen tablets, 250 mg, 100's	Naprosyn	6505-01-061-2198
Oxycodone hydrochloride, aspirin, caffeine, oxycodone terephthalate, and phenacetin tablets, 100's.	Percodan	6505-01-030-9493
Oxycodone hydrochloride, aspirin, caffeine oxycodone terephthalate, and phenacetin tablets, 250's.	Percordan	6505-01-030-9492
Oxyphenbutazone tablets, NF, 100 mg, 1,000's	Tandearil	6505-00-786-8747
Pentazocine hydrochloride tablets, NF, equivalent to 50 mg of pentazocine, 100's.	Talwin	6505-00-180-6030
Pentazocine hydrochloride tablets, NF, equivalent to 50 mg of pentazocine, individually sealed, 100's.	Talwin	6505-01-008-5995
Phenylbutazone tablets, USP, 100 mg, 100's	Butazolidin	6505-00-181-7888
Phenylbutazone tablets, USP, 100 mg, 1,000's	Butazolidin	6505-00-181-7895
Propoxyphene hydrochloride capsules, USP, 65 mg, 500's	Darvon	6505-00-958-2364
Propoxyphene hydrochloride capsules, USP, 65 mg. individually sealed, 100's.	Darvon	6505-00-118-1207
Propoxyphene napsylate and acetaminophen tablets, 30's	Darvocet-N 100	6505-00-111-8364
Propoxyphene napsylate and acetaminophen tablets, 500's	Darvocet-N 100	6505-00-111-8359
Propxyphene napsylate and acetaminophen tablets, individually sealed, 100's.	Darvocet-N 100	6500-00-111-8373
Propoxyphene napsylate and aspirin tablets, 30's	Darvon-N with ASA	6505-00-083-5762
Propoxyphene napsylate and aspirin tablets, 500's	Darvon-N with ASA	6505-00-212-6109
Propoxyphene napsylate tablets, NF, 100 mg, 30's	Darvon-N	6505-00-083-5750
Propoxyphene napsylate tablets, NF, 100 mg, 500's	Darvon-N	6505-00-111-8383
Sodium salicylate tablets, NF, 0.324, gram, 1,000's		6505-00-299-8617
Solmetin sodium tablets, 200 mg, 500's	Tolectin	6505-01-030-3241

PROPOXYPHENE DRUG PRODUCTS IN THE FEDERAL SUPPLY CATALOG

Generic name	Trade name	NSN	Date standardized
Propoxyphene hydrochloride capsules, USP, 65 mg 500's.	Darvon	6505-00-958-2364	January 1965.
Propoxyphene hydrochloride capsules, USP, 65 mg, individually sealed, 100's.	Darvon	6505-00-118-1207	May 1973.
Propoxyphene napsylate tablets, NF, 100 mg, 30's	Darvon-N	6505-00-083-5750	February 1973.
Propoxyphene napsylate tablets, NF, 100 mg, 500's	Darvon-N	6505-00-111-8383	July 1974.
Propoxyphene napsylate and aspirin tablets, 30's	Darvon-N with ASA	6505-00-083-5762	February 1973.
Propoxyphene Napsylate and aspirin tablets, 500's	Darvon-N with ASA	6505-00-212-6109	July 1974.
Propoxyphene napsylate and acetaminophen tablets, 500's.	Darvocet-N 100	6505-00-111-8359	August 1974.
Propoxyphene napsylate and acetaminophen tablets, 30's.	Darvocet-N 100	6505-00-111-8364	August 1974.
Propoxyphene napsylate and acetaminophen tablets, individually sealed, 100's.	Darvocet-N 100	6505-00-111-8373	August 1974.

CENTER FOR HUMAN TOXICOLOGY,
UNIVERSITY OF UTAH,
Salt Lake City, Utah, January 24, 1979.

Dr. WILLIAM Q. STURNER,
Medical Examiner's Office, Department of Health,
Providence, R.I.

DEAR BILL: This letter will formally introduce to you Dr. Yale Caplan who is serving as a consultant forensic toxicologist to the Center For Human Toxicology.

The purpose of our joint activity is to assist the government, particularly the FDA Drug Abuse Advisory Committee and Senator Gaylord Nelson's Congressional Committee on various aspects of propoxyphene toxicity.

The CHT's assistance has been requested because of our past record in this field but unfortunately, time constraints have made it impossible for me to fulfill their requests alone. Hence, the CHT has engaged Dr. Caplan, Dr. Garriott and Mr. Shaw for this purpose. I know of your personal concerns about the involvement of propoxyphene in medico-legal cases and, therefore, it seemed vital to me that we obtain information from your office and benefit from your opinions. I ask that you cooperate with Dr. Caplan and thereby assist the appropriate government offices to have before them as much authenticated data as possible concerning this drug.

Thanks for your assistance. Best personal regards.

Yours sincerely,

BRYAN S. FINKLE, Ph. D.,
Director.

DARVON RELATED DEATHS

1974:
131 Propoxyphene (Suicide)

1975:
1926 Propoxyphene (Suicide)
2234 Darvon, Propoxyphene (Suicide)
2367 Propoxyphene (Unclassified)
2981 Propoxyphene (Undetermined)

1976:
0058 Propoxyphene (Unclassified)
0200 Propoxyphene (Suicide)
0257 Propoxyphene (Unclassified)
0330 Propoxyphene (Suicide)
0589 Darvon (Suicide)
1033 Propoxyphene (Natural)
1172 Propoxyphene (Unclassified)
1266 Propoxyphene (Suicide)
1870 Propoxyphene (Suicide)
2046 Propoxyphene (Suicide)
2118 Propoxyphene (Unclassified)
2303 Propoxyphene (Unclassified)
2405 Propoxyphene, Darvon (Suicide)
2496 Propoxyphene (Unclassified)
3185 Propoxyphene (Unclassified)

1977:
0191 Nor-propoxyphene (Suicide)
0307 Nor-propoxyphene (Unclassified)
0440 Propoxyphene (Suicide)
0564 Nor-propoxyphene (Accident)
0738 Propoxyphene (Suicide)
1403 Nor-propoxyphene (Accident)
1406 Propoxyphene (Suicide)
1534 Nor-propoxyphene (Homicide)
1641 Nor-propoxyphene (Natural)
1701 Propoxyphene (Accident)
1783 Propoxyphene (Accident)
1892 Propoxyphene (Unclassified)
2168 Propoxyphene (Suicide)
2182 Propoxyphene (Suicide)
2412 Propoxyphene (Suicide)
2595 Propoxyphene (Suicide)
3182 Propoxyphene (Suicide)

1978:
0012 Propoxyphene (Suicide)
0500 Propoxyphene (Suicide)
0819 Propoxyphene (Accident)
1028 Propoxyphene (Unclassified)
1349 Propoxyphene (Suicide)
1596 Nor-propoxyphene (Natural)
2046 Propoxyphene (Unclassified)
3023 Propoxyphene (Suicide)
3461 Nor-propoxyphene (Natural)

1974: 1 Suicide.
1975: (4) 2 Suicides; 1 Unclassified; 1 Undetermined.
1976: (15) 1 Natural; 7 Suicides; 7 Unclassified.
1977: (17) 4 Accidents; 1 Homicide (GSW); 1 Natural; 9 Suicides; 2 Unclassified.
1978: (9) 1 Accident; 2 Naturals; 4 Suicides; 2 Unclassified.
Total number of deaths in a 5-year period is 46.

Rec'd 2/2/76

M 205-756 ME 2234-75

BLOOD { 0.91 mg% PROPOX
0.016 mg% AMPHETAMINE
56.0 mg% SALICYLATE

URINE { 3.3 mg% PROPOXYPHENE
56 mg% SALICYLATES

ST. C 50 ml { 1.5 mg% PROPOXYPHENE
0.09 mg SALICYLATE
0.10 mg AMITRIPTYLINE

4 total
4 less
46 fatal

M-244-756 ME 2367-75

BLOOD { 0.44 mg% PROPOX
1.95 mg% PHENOBARBITAL

URINE { 2.8 mg% PROPOXYPHENE
21.0 mg% PHENOBARBITAL

S.C. 12 cm3 44.0 mg PROPOXYPHENE

15

M-370-756 ME 2981-75

BLOOD 0.39 mg% PROPOX
0.43 mg% DILANTIN
0.97 mg% PHENOBARB

URINE 0.62 mg% PROPOX
TRACE DILANTIN
1.07 mg% PHENOBARBITAL

S C 200 ml 2 E.3 mg PROPOX
TRACE DILANTIN
TRACE PHENOBARBITAL

4-381-756 ME 0058-76

BLOOD 1.5 mg% PROPOX 0.07% ETOH

URINE 18.0 mg% " 0.66% ETOH

SC (3 ml) 0.5 mg

Bile Duct (5 ml) 8.6 mg

LIVER 18.3 mg% 0.07% ETOH Rib.

KIDNEY 11.6 mg%

1 Copy to Sidney Wolfe

1/76

TM-413-789 ME 0200-76

BLOOD
- 0.30 mg% PROPOX
- 0.04 mg% SECOBARB
- 5.66 mg% PHENOBARB

URINE
- 5.84 mg% PROPOX
- 0.02 mg% SECOBARB
- 2.83 mg% PHENOBARB

S.C. 20 ml
- 0.56 mg% PROPOX
- TRACE SECOBARB
- 0.05 mg% PHENOBARB

TM-424-756 ME 0257-76

BLOOD
- 0.62 mg% PROPOX
- 1.19 mg% NOR PROPOX
- 0.37 mg% PHENOBARB
- 0.98 mg% DILANTIN

URINE
- 0.98 mg% PROPOX
- 0.95 mg% NOR PROPOX
- 0.55 mg% PHENOBARB

LIVER
- 1.6 mg% PROPOX
- 0.20 mg% NORPROPOX

SC 150 ml 289 mg PROPOX

BILE
- 0.27 mg% PROPOX
- 39.8 mg% NOR PROPOX

TM-445-786 ME 0330-76

BLOOD 1.14 mg% PROPOX

URINE 5.4 mg% PROPOX

LIVER 10.8 mg% PROPOX

S.C. 120 ml 315.5 mg PROPOX

TM-605-756 ME 1033-76

BLOOD
- 0.02 mg% PROPOX
- 0.10 mg% NOR PROPOX

URINE
- 0.55 mg% PROPOX
- 8.34 mg% NOR PROPOX
- 0.826 mg% PROPOX

LIVER
- 0.15 mg% NOR PROPOX

SC. POS – PROPOX

TM-630-756 ME 1172-76

BLOOD { 0.4 mg% PROPOX
0.77 mg% NOR PROPOX
3.34 mg% CHLORDIAZEPOXIDE

URINE { 4.15 mg% PROPOX
26.2 mg% NOR PROPOX
6.17 mg% CHLORDIAZEPOXIDE

LIVER { 3.69 mg% PROPOX
4.57 mg% NOR PROPOX
2.22 mg% CHLORDIAZEPOXIDE

FAT. { 2.05 mg% PROPOX
0.86 mg% CHLORDIAZEPOXIDE

MUSC. { 0.11 mg% PROPOX
0.24 mg% NOR PROPOX
0.21 mg% CHLORDIAZEPOXIDE

S.C. 25 ml { 3.21 mgs PROPOX
0.026 mgs NOR PROPOX
3.73 mgs CHLORDIAZEPOXIDE

1-14-76

TM-653-756 ME 1266-76 1266

BLOOD { 0.12 mg% PROPOX
0.13 mg% NOR PROPOX

URINE { 0.35 mg% PROPOX
6.55 mg% NOR PROPOX

LIVER { 1.53 mg% PROPOX
0.10 mg% NOR PROPOX

SC (90 ml) 406.0 mgs PROPOX

5-12-76

M-24-767 ME 1725-76

BLOOD { 0.38 mg% PROPOX .07% ETOH
0.15 mg% NOR PROPOX

URINE { 4.66 mg% PROPOX .10% ETOH
7.07 mg% NORPROPOX

LIVER { 1.16 mg% PROPOX
1.09 mg% NOR PROPOX

SC (30 ml) 110.8 mgs

6-1-76

M-62-767 ME 1870-76

BLOOD { 1.90 mg% PROPOX 0.05% ETOH
0.26 mg% NOR PROPOX

URINE { 2.5 mg% PROPOX 0.15% ETOH
1.16 mg% NOR PROPOX

LIVER { 24.0 mg% PROPOX .08% ETOH BILE
0.40 mg% NOR PROPOX

SC 8 cc/ml 8.58 mgs

AUG '76

M-112-767	ME 2046-76	BLOOD	0.836 mg% PROPOX NEG % NOR PROPOX	
		URINE	76.0 mg% SALICYLATES	
M-127-767	ME 2118-76	BLOOD	0.42 mg% PROPOX 0.17 mg% NOR PROPOX	0.05% ETOH
		URINE	1.83 mg% PROPOX 0.53 mg% NOR PROPOX	0.14% ETOH
		LIVER	5.78 mg% PROPOX 0.15 mg% NOR PROPOX	
		SC (32 ml)	1.69 mg	
M-141-767	ME 2184-76	BLOOD	0.03 mg% PROPOX 0.09 mg% NOR PROPOX TRACE AMITRIPTYLINE	
		URINE	0.69 mg% PROPOX 2.16 mg% NOR PROPOX	
M-173-767	ME 2303-76	BLOOD	0.17 mg% PROPOX 0.59 mg% NOR PROPOX 0.01 mg% PHENIRAMINE 0.27 mg% ETHCHLORVYNOL	
		URINE	0.72 mg% PROPOX 4.07 mg% NOR PROPOX 0.09 mg% PHENIRAMINE 11.4 mg% ETHCHLORVYNOL	
		LIVER	0.075 mg% PROPOX 0.712 mg% NOR PROPOX 0.056 mg% PHENIRAMINE 1.0 mg% ETHCHLORVYNOL	
		SC	17.9 mg% PROPOX 0.37 mg% NOR PROPOX 0.62 mg% PHENIRAMINE	
M-201-767	ME 2405-76	BLOOD	0.33 mg% PROPOX	
		URINE	0.07 mg% PROPOX 2.92 mg% NOR PROPOX 23.9 mg% SALICYLATE 0.06 mg% CODEINE COCAINE + (HIM)	
		LIVER	0.018 mg% PROPOX 0.88 mg% CODEINE	
		SC	7.48 mg% PROPOX	

TM 217-767 ME 2496-76

M. BLOOD
- 0.64 mg% PROPOX
- 0.05 mg% NOR PROP X

0.13% ETOH

PM BLOOD
- 0.13 mg% PROPOX
- 0.33 mg% NOR PROPOX
- 0.08 mg% MORPHINE

0.13% ETOH

URINE
- 0.99 mg% PROPOX
- 2.19 mg% NOR PROPOX
- 6.1 mg% MORPHINE

0.18% ETOH

LIVER
- 1.57 mg% PROPOX
- 2.03 mg% NOR PROPOX

BILE
- 4.6 mg% MORPHINE
- 7.3 mg% PROPOX

0.18% ETOH

ST. C.
- 0.03 mg NOR PROPOX
- 3.5 mg MORPHINE

SM. INT
- 7.6 mg PROPOX
- 0.36 mg NOR PROPOX
- 0.29 mg MORPHINE

2/76
M-323-767 ME 2956-76

BLOOD
- TRACE PROPOX
- TRACE PHENETRAZINE
- 0.03 mg% ETHCHLORVYNOL
- 0.008 mg% MORPHINE

URINE
- 0.167 mg% PROPOX
- 0.90 mg% NOR PROPOX
- 3.9 mg% PHENETRAZINE
- 91.5 mg% ETHCHLORVYNOL
- 0.38 mg% MORPHINE

LIVER
- 0.03 mg% PROPOX
- 1.6 mg% ETHCHLORVYNOL

BILE
- 3.6 mg% MORPHINE

M-372-769 ME 3185-76

BLOOD
- 0.64 mg% PROPOX
- 1.49 mg% NOR PROPOX
- 0.16 mg% AMOBARB
- 0.04 mg% SECOBARB

URILE
- 0.118 mg% PROPOX
- 16.81 mg% NOR PROPOX
- 1.03 mg% AMOBARB
- 0.34 mg% SECOBARB

BC 144 mi
- 11.6 mg% PROPOX
- 2.11 mg% NOR PROPOX
- 0.50 mg% AMOBARB
- 0.24 mg% SECOBARB

TM 468-767	C191-77	Blood / Urine	0.0 Blood: Naproxen; 2.49 mg% Urine Naproxen	ANALYTICAL ERROR
TM-439-767	D307-77	Blood	0.02 mg% Propox; 0.18 mg% Naproxen; 0.09 mg% Darvon	
		LIVER	0.20 mg% Propox; 0.42 mg% Naproxen; 0.92 mg% SECOBARB	
		KID	0.24 mg% PROPOX; 0.52 mg% NOR PROPOX; 0.35 mg% SECO BARB	
TM-460-767	ME 0440-77	BLOOD	1.27 mg% PROPOX; 1.3 mg% NOR PROPOX	0.09% ETOH
		URINE	0.28 mg% PROPOX; 0.73 mg% NOR PROPOX	0.16% ETOH
		LIVER	18.1 mg% PROPOX; 2.85 mg% NOR PROPOX	
		SC (femal)	3.73 mg% PROPOX; 0.91 mg% NOR PROPOX	
TM-489-789	ME 0564-77	BLOOD	0.03 mg% NOR PROPOX	0.23% ETOH
		URINE	0.16 mg% "	0.38% ETOH
TM-530-767	ME 0703-77	URINE	0.24 mg% NOR PROPOX	0.08 ETOH 1st; 0.09 % ETOH 2nd
TM-528-767	0737-77	BLOOD	Trace PROPOX	0.18% ETOH
		URINE	0.06 mg% PROPOX; 0.31 mg% NOR PROP	0.20% ETOH
		LIVER	0.06 mg% PROPOX	
		SC (3 areas)	0.124 mg% PROPOX	
TM 686-767	ME 1406-77	BLOOD	0.46 mg% PROPOX; 0.89 mg% NOR PROPOX; 0.63 mg% BUTALBITAL	0.13% ETOH
TM-711-767	ME 1534-77	BLOOD	0.03 mg% NOR PROPOX	
		URINE	0.93 mg% NOR PROPOX	

T.M-733-767	MC 1661-77	Blood	0.1 mg % NOR PROPOX
T.M-746-767	MC 1641-77	Bl.	0.02 mg % NOR PROPOX
		Ur	0.8 mg % "
T.M-4-778	MC 1701-77	Blood	0.13 mg % PROPOX 0.39 mg % NOR PROPOX 0.33 mg % ETHYLENOXALL
		URINE	2.34 mg % PROPOX 8.76 mg % NOR PROPOX 5.39 mg % ETHYLENOXALL
		LIVER	1.50 mg % PROPOX 0.22 mg % NOR PROPOX 1.12 mg % ETHYLENOXALL
		SM. INT. 30 cm	0.32 mg % PROPOX 0.05 mg % NOR PROPOX
T.M-29-778	MC 1783-77	BLOOD	0.17 mg % PROPOX 0.74 mg % NOR PROPOX
		URINE	4.63 mg % PROPOX 8.73 mg % NOR PROPOX
T.M-57-778	1897-77	BLOOD	0.24 mg % PROPOX 0 NOR PROPOX 0.19% BETOX 42.1 mg % SALICYLATE 5.19 mg % CAFFEINE TRACE PHENACETIN
		LIVER	5.39 mg % PROPOX 1.19 mg % NOR PROPOX
T.M-127-778	MC 2168-77	BLOOD	0.23 mg % PROPOX 0.41 mg % NOR PROPOX
		URINE	4.35 mg % PROPOX 23.1 mg % NOR PROPOX
		LIVER	3.7 mg % PROPOX 0.9 mg % NOR PROPOX
		S.C (9cm)	1446 mg PROPOX 3.06 mg NOR PROPOX
M-132-778	MC 2182-77	BLOOD	4.66 mg % PROPOX 0.3 mg % NOR PROPOX
		LIVER	4.93 mg % PROPOX 3.05 mg % NOR PROPOX
		SC (5cm)	81.6 mg PROPOX 0.5 mg NOR PROPOX

M-177-77	ME 2412-77	BLOOD	0.01 mg% PROPOX 0.38 mg% ACR PROPOX 0.40 mg% AMITRIPTYLINE
		URINE	0.12 mg% PROPOX 2.71 mg% ACR PROPOX 0.18 mg% AMITRIPTYLINE
M-216-77	ME 2395-77	BLOOD	0.14 mg% PROPOX 0.54 mg% ACR PROPOX 0.07 mg% SE CODEINE
		URINE	2.38 mg% PROPOX 14.04 mg% ACR PROPOX 0.11 mg% SECOBARB
		SI (blood)	44.4 mg% PROPOX 16.4 mg% ACR PROPOX
M-320-77	ME 2182-77	BLOOD	1.84 mg% NORPROPOX 0 PROPOX
		URINE	2.2 mg% PROPOX 2.41 mg% ACR PROPOX
M-397-77	ME 012-78	BLOOD	0.05 mg% PROPOX TRACE ACR PROPOX 0.03 mg% QUINIDINE
		URINE	0.45 mg% PROPOX TRACE NORPROP 4.35 mg% QUINIDINE 0.013 % ACETONE
M-449-77	ME 0500-78	BLOOD & Urine	PROPOX & PHENOBARB
M-526-77	ME-1698-78	BLOOD	1.33 mg% PROPOX 5.89 mg% NOR PROP 2.74 mg% PHENOBARB 0.09 mg% DILANTIN
		URINE	2.44 mg% PROPOX 13.78 mg% ACR PROPOX 0.30 mg% PHENOBARB
		SE	4.60 mg% PROPOX 0.41 mg% ACR PROPOX 0.37 mg% PHENOBARB
		H-T. E.	0.64 mg% PROPOX 0.69 mg% ACR PROP 0.27 mg% PHENOBARB

TM-41-789	MC 2046-78	Blood	0.09 mg % PROPOX 0.66 mg % NOR PROPOX	0.09% ETOH
		URINE	0.35 mg % PROPOX 0.28 mg % NOR PROPOX	0.15% ETOH
		LIVER	13.21 mg % PROPOX 2.66 mg % NOR PROPOX	
		KIDNEY	1.38 mg % PROPOX 0.28 mg % NOR PROPOX	
		LUNG	4.38 mg % PROPOX 2.86 mg % NOR PROPOX	
		SC	3.74 mg PROPOX	
		INT. C	8.0 mg PROPOX 0.42 mg NOR PROPOX	
TM-203-789	MC 2948-78	BLOOD	0.04 mg % PROPOX 0.09 mg % NOR PROPOX	0.28% ETOH
		URINE	0.16 mg % PROPOX 1.09 mg % NOR PROPOX	0.34% ETOH
TM 219-789	MC 3033-78	BLOOD	1.20 mg % PROPOX 1.25 mg % NOR PROPOX 6.25 mg % AMITRIPTYLINE	0.11% ETOH
		URINE	0.10 mg % PROPOX 0.43 mg % NOR PROPOX 0.01 mg % AMITRIPTYLINE	0.11% ET
TM-291-789	MC 3161-78	BLOOD	0.25 mg % PROPOX 0.13 mg % NOR PROPOX 2.39 mg % PROPOX	0.18% ETOH
		URINE	4.31 mg % NOR PROPOX	0.24% ETOH

Rec'd 2/2/79

M 205-756 ME 2234-75

BLOOD { 0.91 mg% PROPOX
0.016 mg% AMITRIPTYLINE
56.8 mg% SALICYLATE

URINE { 3.3 mg% PROPOXYPHENE
56 mg% SALICYLATES

ST. C 50 cc { 1.5 mg% PROPOXYPHENE
0.19 mg SALICYLATE
0.10 mg AMITRIPTYLINE

4 total
4 cases
46 fatal

4-244-756 ME 2367-75

BLOOD { 0.44 mg% PROPOX
1.95 mg% PHENOBARBITAL

URINE { 2.5 mg% PROPOXYPHENE
2.0 mg% PHENOBARBITAL

S.C 12 cc 44.0 mg PROPOXYPHENE

65

M-370-756 ME 2981-75

BLOOD 0.39 mg% PROPOX
0.43 mg% DILANTIN
0.97 mg% PHENOBARB

URINE 0.62 mg% PROPOX
TRACE DILANTIN
1.07 mg% PHENOBARBITAL

S C 200 ml 28.3 mg PROPOX
TRACE DILANTIN
TRACE PHENOBARBITAL

1-381-756 ME 0058-76

BLOOD 1.5 mg% PROPOX 0.07% ETOH
URINE 18.0 mg% " 0.06% ETOH
SC (3 ml) 0.5 mg
Bar Dr (5 ml) 8.6 mg
LIVER 18.3 mg% 0.07% ETOH Rib.
KIDNEY 11.6 mg%

1 Copy to Sidney Wolfe

1/76

TM-413-789 ME 0200-76

BLOOD
- 0.30 mg% PROPOX
- 0.04 mg% SECOBARB
- 5.66 mg% PHENOBARB

URINE
- 5.84 mg% PROPOX
- 0.08 mg% SECOBARB
- 2.83 mg% PHENOBARB

S.C. 20 ml
- 0.56 mg% PROPOX
- TRACE SECOBARB
- 0.05 mg% PHENOBARB

TM-424-756 ME 0257-76

BLOOD
- 0.82 mg% PROPOX
- 1.19 mg% NOR PROPOX
- 0.37 mg% PHENOBARB
- 8.98 mg% DILANTIN

URINE
- 0.98 mg% PROPOX
- 0.95 mg% NOR PROPOX
- 0.55 mg% PHENOBARB

LIVER
- 1.6 mg% PROPOX
- 0.20 mg% NORPROPOX

SC 100 ml 289 mg PROPOX

BILE
- 0.27 mg% PROPOX
- 39.8 mg% NOR PROPOX

TM-445-786 ME 0330-76

BLOOD 1.14 mg% PROPOX

URINE 5.4 mg% PROPOX

LIVER 10.8 mg% PROPOX

S.C. 170 ml 315.5 mg PROPOX

TM-605-756 ME 1033-76

BLOOD
- 0.02 mg% PROPOX
- 0.10 mg% NOR PROPOX

URINE
- 8.55 mg% PROPOX
- 8.34 mg% NOR PROPOX
- 0.826 mg% CPROPOX

LIVER
- 0.15 mg% NOR PROPOX

SC. POB – PROPOX

TH-630-756 ME 1172-76

BLOOD { 0.14 mg% PROPOX; 6.77 mg% NOR PROPOX; 3.34 mg% CHLORDIAZEPOXIDE

URINE { 4.15 mg% PROPOX; 26.2 mg% NOR PROPOX; 6.17 mg% CHLORDIAZEPOXIDE

LIVER { 3.69 mg% PROPOX; 4.51 mg% NOR PROPOX; 2.22 mg% CHLORDIAZEPOXIDE

FAT { 2.05 mg% PROPOX; 0.86 mg% CHLORDIAZEPOXIDE

MUSC { 0.11 mg% PROPOX; 0.24 mg% NOR PROPOX; 0.21 mg% CHLORDIAZEPOXIDE

SQ. 25 ml { 3.21 mgs PROPOX; 0.026 mgs NOR PROPOX; 3.73 mgs CHLORDIAZEPOXIDE

1144-76

TM-653-756 ME 1266-76 1266

BLOOD { 0.12 mg% PROPOX; 0.13 mg% NOR PROPOX

URINE { 0.35 mg% PROPOX; 6.52 mg% NOR PROPOX

LIVER { 1.53 mg% PROPOX; 0.10 mg% NOR PROPOX

SQ (90 ml) 406.0 mgs PROPOX

5 LL '76

M-24-767 ME 1725-76

BLOOD { 0.38 mg% PROPOX; 0.15 mg% NOR PROPOX — .07% ETOH

URINE { 4.66 mg% PROPOX; 7.07 mg% NOR PROPOX — .10% ETOH

LIVER { 1.16 mg% PROPOX; 1.09 mg% NOR PROPOX

SQ (360 ml) 110.8 mgs

12 '76

M-62-767 ME 1870-76

BLOOD { 1.90 mg% PROPOX; 0.26 mg% NOR PROPOX — 0.05% ETOH

URINE { 2.5 mg% PROPOX; 1.16 mg% NOR PROPOX — 0.15% ETOH

LIVER { 24.0 mg% PROPOX; 0.40 mg% NOR PROPOX — .08% ETOH BILE

SQ 800 ml 8.58 mgs

M-112-767	ME 2046-76	BLOOD	0.836 mg% PROPOX NEG NOR PROPOX	
		URINE	76.0 mg% SALICYLATES	
M-127-767	ME 2118-76	BLOOD	0.42 mg% PROPOX 0.17 mg% NOR PROPOX	0.05% ETOH
		URINE	1.83 mg% PROPOX 0.53 mg% NOR PROPOX	0.14% ETOH
		LIVER	5.78 mg% PROPOX 0.15 mg% NOR PROPOX	
		SC (32 ml)	1.69 mg	
M-141-767	ME 2184-76	BLOOD	0.03 mg% PROPOX 0.09 mg% NOR PROPOX TRACE AMITRIPTYLINE	
		URINE	0.69 mg% PROPOX 2.16 mg% NOR PROPOX	
M-173-767	ME 2303-76	BLOOD	0.17 mg% PROPOX 0.59 mg% NOR PROPOX 0.06 mg% PHENIRAMINE 0.27 mg% ETHCHLORVYNOL	
		URINE	0.72 mg% PROPOX 4.07 mg% NOR PROPOX 0.09 mg% PHENIRAMINE 11.4 mg% ETHCHLORVYNOL	
		LIVER	0.075 mg% PROPOX 0.712 mg% NOR PROPOX 0.056 mg% PHENIRAMINE 1.0 mg% ETHCHLORVYNOL	
		SC	17.9 mg% PROPOX 0.37 mg% NOR PROPOX 0.62 mg% PHENIRAMINE	
M-201-767	ME 2405-76	BLOOD	0.33 mg% PROPOX	
		URINE	0.07 mg% PROPOX 0.92 mg% NOR PROPOX 23.9 mg% SALICYLATE 0.66 mg% CODEINE ECGONINE + (HIM)	
		LIVER	0.018 mg% PROPOX 0.88 mg% CODEINE	
		SC	7.48 mg% PROPOX	

TM 217-767 ME 2496-76	M. BLOOD	0.64 mg% PROPOX 0.09 mg% NORPROPOX	0.15% ETOH
	PA BLOOD	0.13 mg% PROPOX 0.133 mg% NORPROPOX 0.08 mg% MORPHINE	0.13% ETOH
	URINE	0.99 mg% PROPOX 2.19 mg% NORPROPOX 6.1 mg% MORPHINE	0.18% ETOH
	LIVER	1.57 mg% PROPOX 2.63 mg% NORPROPOX	
	BILE	4.6 mg% MORPHINE 7.3 mg% PROPOX	0.18% ETOH
	ST. C.	0.034 mg NORPROPOX 3.5 mg MORPHINE	
	SM. INT	7.6 mg PROPOX 0.36 mg NORPROPOX 0.99 mg MORPHINE	
2/76 M-323-767 ME 2956-76	BLOOD	TRACE PROPOX TRACE PHENMETRAZINE 0.162 mg% ETHCHLORVYNOL 0.005 mg% MORPHINE	
	URINE	0.167 mg% PROPOX 0.90 mg% NORPROPOX 3.9 mg% PHENMETRAZINE 91.5 mg% ETHCHLORVYNOL 0.132 mg% MORPHINE	
	LIVER	0.03 mg% PROPOX 1.6 mg% ETHCHLORVYNOL	
	BILE	3.6 mg% MORPHINE	
M-372-769 ME 3185-76	BLOOD	0.64 mg% PROPOX 1.49 mg% NORPROPOX 0.16 mg% AMOBARB 0.64 mg% SECOBARB	
	URINE	0.18 mg% PROPOX 16.81 mg% NORPROPOX 1.03 mg% AMOBARB 0.34 mg% SECOBARB	
	SC 144#	11.6 mg% PROPOX 0.11 mg% NORPROPOX 0.50 mg% AMOBARB 5.24 mg% SECOBARB	

TM 468-767	0191-77	Blood / Urine	0.81 mg% Meprobamate; 2.49 mg% Meprobamate	Marijuana OD
TM-439-767	0307-77	Blood	0.04 mg% Propoxy; 0.18 mg% Meprobamate; 0.09 mg% Librium	
		Liver	0.20 mg% Propoxy; 0.42 mg% Meprobamate; 0.95 mg% Secobarb	
		Kid	0.24 mg% Propoxy; 0.59 mg% Acetaminophen; 0.35 mg% Secobarb	
TM-460-767	ME 0440-77	Blood	1.27 mg% Propoxy; 1.3 mg% Acetaminophen	0.09% Etoh
		Urine	0.28 mg% Propoxy; 0.73 mg% Acetaminophen	0.16% Etoh
		Liver	18.1 mg% Propoxy; 2.55 mg% Acetaminophen	
		Sc (femur)	373 mg% Propoxy; 0.91 mg% Acetaminophen	
TM-489-769	ME 0564-77	Blood	0.03 mg% Acetaminophen Propoxy	0.22% Etoh
		Urine	0.16 mg% "	0.38% Etoh
TM-520-767	ME 0763-77	Urine	0.24 mg% Acetaminophen Propoxy	0.08 Etoh Ser; 0.09 % Etoh Urine
TM-528-767	0737-77	Blood	Trace Present	0.18% Etoh
		Urine	0.06 mg% Propoxy; 0.31 mg% Acetaminophen	0.35% Etoh
		Liver	0.06 mg% Propoxy	
		Sc (femur)	0.124 mg Propoxy	
TM-686-767	ME 1406-77	Blood	0.46 mg% Propoxy; 0.89 mg% Acetaminophen; 0.63 mg% Butalbital	0.13% Etoh
TM-711-767	ME 1534-77	Blood	0.03 mg% Acetaminophen	
		Urine	0.93 mg% Acetaminophen	

T.M-733-767	ME 1661-77	Blood	0.15 mg % ALK PHOS
T.M-746-767	ME 1641-77	Blood	0.62 mg % ALK PHOS
		Urine	0.86 mg % "
T.M-4-778	ME 1761-77	Blood	0.75 mg % PHOS 6.39 mg % ALK PHOS 0.33 mg % ETHANOLAMINE
		URINE	2.34 mg % PHOS 8.76 mg % ALK PHOS 5.39 mg % ETHANOLAMINE
		LIVER	1.56 mg % PHOS 0.22 mg % ALK PHOS 1.12 mg % ETHANOLAMINE
		SH. INT. 30 min	0.32 mg % PHOS 0.05 mg % ALK PHOS
T.M 29-778	ME 1783-77	BLOOD	0.17 mg % PHOS 0.74 mg % ALK PHOS
		URINE	4.65 mg % PHOS 8.75 mg % ALK PHOS
T.M-53-778	1897-77	BLOOD	0.29 mg % PHOS 0 ALK PHOS 42.1 mg % SALICYLATE 5.89 mg % CAFFEINE TRACE PHENACETIN 0.19 % BENZ
		LIVER	5.39 mg % PHOS 1.19 mg % ALK PHOS
T.M-127-778	ME 2168-77	BLOOD	0.23 mg % PHOS 0.41 mg % ALK PHOS
		URINE	4.35 mg % PHOS 23.1 mg % ALK PHOS
		LIVER	3.7 mg % PHOS 0.9 mg % ALK PHOS
		SC (9 mo)	144 mg PHOS 3.0 mg ALK PHOS
T.M-132-778	ME 2182-77	BLOOD	4.66 mg % PHOS 0.3 mg % ALK PHOS
		LIVER	6.95 mg % PHOS 3.05 mg % ALK PHOS
		SC (5 mo)	81.6 mg PHOS 0.5 mg ALK PHOS

M-[illegible]	ME 2412-77	BLOOD	0.01 mg% PROPOX 0.38 mg% NOR PROPOX 0.40 mg% NAPHTHYLENE
		URINE	0.12 mg% PROPOX 2.71 mg% NOR PROPOX 0.12 mg% NAPHTHYLENE
M-216-78	ME 239597	BLOOD	0.14 mg% PROPOX 0.54 mg% NOR PROPOX 0.07 mg% SEC BARB
		URINE	2.58 mg% PROPOX 14.04 mg% NOR PROPOX 0.11 mg% SEC BARB
		STOMACH	44.4 mg PROPOX 16.4 mg NOR PROPOX
M-330-78	ME 3182-77	BLOOD	1.84 mg% NORPROPOX 0 PROPOX
		URINE	2.2 mg% PROPOX 2.4 mg% NORPROPOX
M-377-78	ME 612-78	BLOOD	0.05 mg% PROPOX TRACE NORPROPOX 0.03 mg% VALIUM
		URINE	0.45 mg% PROPOX TRACE NORPROP 4.35 mg% VALIUM 0.013 % ACETONE
M-449-78	ME 0500-78	BLOOD & URINE	PROPOX & METABARB
M-526-78	ME-1028-78	BLOOD	1.33 mg% PROPOX 5.89 mg% NOR PROP 7.74 mg% PHENOBARB 0.09 mg% DILANTIN
		URINE	2.44 mg% PROPOX 13.78 mg% NOR PROPOX 0.37 mg% PHENOBARB
		SC	4.60 mg PROPOX 0.41 mg NOR PROPOX 0.37 mg PHENOBARB
		I.V. C.	0.64 mg PROPOX 0.054 mg NORPROPOX 0.37 mg PHENOBARB

TM-41-789	ME 2046-78	Blood	0.09 mg % PROPOX 0.66 mg % NOR PROPOX	0.09% ETOH
		URINE	0.35 mg % PROPOX 0.24 mg % NOR PROPOX	0.15% ETOH
		LIVER	13.28 mg % PROPOX 2.66 mg % NOR PROPOX	
		KIDNEY	1.38 mg % PROPOX 0.28 mg % NOR PROPOX	
		LUNG	4.38 mg % PROPOX 2.86 mg % NOR PROPOX	
		SC	3.74 mg PROPOX	
		INT. C	8.0 mg PROPOX 6.42 mg NOR PROPOX	
TM-203-789	ME 2948-78	BLOOD	0.04 mg % PROPOX 0.09 mg % NORPROPOX	0.2E% ETOH
		URINE	0.16 mg % PROPOX 1.09 mg % NORPROPOX	0.34% ETOH
TM 219-789	ME 3023-78	BLOOD	1.20 mg % PROPOX 1.25 mg % NOR PROPOX 6.25 mg % AMITRIPTYLINE	0.21% ETOH
		URINE	0.10 mg % PROPOX 0.43 mg % NOR PROPOX 0.01 mg % AMITRIPTYLINE	0.27% ET
TM-291-789	ME 3161-78	BLOOD	0.23 mg % PROPOX 6.13 mg % AMITRIPTY 2.39 mg % PROPOXY 4.31 mg % NORPROPOXY	0.18% ETOH 0.24% ETOH
		URINE		

THE UNIVERSITY OF KANSAS MEDICAL CENTER,
COLLEGE OF HEALTH SCIENCES AND HOSPITAL,
Kansas City, Kans., January 26, 1979.

Senator GAYLORD NELSON,
Senate Small Business Committee, Russell Senate Office Building,
Washington, D.C.

DEAR SENATOR NELSON: Since I was unable to arrange for Committee time in order to present testimony concerning the future of propoxyphene, I would like to avail myself of the opportunity to submit written comments for consideration by the Committee and inclusion in the record of Committee proceedings.

Past experience with federal hearings concerned with health matters has given me the impression that all too often the viewpoint of one interested group is missing—that of practicing physicians who are directly responsible to and for the patient. This perspective might provide information to the Committee which is not available from pharmaceutical company officers, research investigators or physicians who, because of lack of "real life" practice experience, must generate attitudes on the basis of something less. I suspect that considerable pressures are exerted upon committees such as yours by a wide variety of individuals whose knowledge and experience is purely theoretical rather than being based on practical experience.

The background for my comments includes 26 years of practice of family medicine in rural Colorado. This practice included almost the total spectrum of human health problems, ranging from being responsible for major surgery and obstetrics to caring for the multiple aches and discomforts associated with daily life.

The problem of relieving pain—acute or chronic—arose daily, and over the years I have used many agents for this purpose. My choice of agent depended on the response of my patients rather than the advertised claims of the manufacturer. Many different compounds were used and some were discarded as being ineffective or likely to produce side effects. Before writing any analgesic prescriptions, factors such as probable severity of pain, patient drug idiosyncracy or allergy, other medications being taken, alcohol intake, psychic stability (especially depressive conditions or addictive history) and probable duration of discomfort were all considered. This resulted in my need for a variety of analgesics so that each prescription could be tailored to meet the needs of the individual patients.

My personal "analgesic armentarium" which worked quite effectively for me in something over a half million patient contacts is as follows:

Comparative strength	Agent	Watch for
Weakest analgesic	Aspirin	Allergy, GI upset.
	Tylenol	Teenage suicide agent.
Strongest analgesic	Propoxyphene compounds	Alcoholism, concurrent tranquilizers.
Stronger yet	Codeine (½–1 gr) compounds	10 percent nausea plus vomiting, constipation
Strongest	Meperidine (in patient)	Frequent nausea plus vomiting.
	Morphine (in patient)	Do.

Each agent is valuable under certain conditions, and no one of them is satisfactory in all cases. Propoxyphene compounds fill a definite analgesic niche which OTC agents are too weak to fill. They are effective and have a low incidence of unpleasant side effects. Unavailability of propoxyphene compounds would probably result in increased use of the more potent and addictive narcotic drugs, since the OTC agents lack sufficient pain relieving qualities to serve as a substitute. Since many patients with chronic illnesses (rheumatoid arthritis, chronic back pain, etc.) require propoxyphene compounds on a long-term basis, reasonably simple prescription access should exist. I believe that this presents minimal hazard in properly selected patients, since I have never seen a major threat to life or health of a patient in this category due to accidental or purposeful overdose. Propoxyphene compounds are not a panacea for all patients or all pains; they do, however, provide a prescriber with effective alternatives and the ability to match the potency of the medication to the pain.

My other area of concern is the ever increasing intrusion of the government into the practice of medicine with the resultant detrimental effect upon the

physician-patient relationship. I must echo the words of President Carter who this week in his State of the Union Address, commented that government regulation of private lives must be decreased. Such regulation is particularly disturbing when it originates with physicians who by virtue of a medical degree become instant experts on health care. Some regulation is obviously necessary when the public health and welfare are genuinely at risk, but when regulation of drugs is being considered, I beg for inclusion of the people who use the compounds, who know from experience if they are effective and who are ultimately responsible for the welfare of patients, in the policy making process.

I thank the Committee for consideration of my comments and the demonstrated interest in assuring the availability of safe, effective and reasonably accessible therapeutic agents to the public. Should I be able to supply any further information, I will be glad to do so.

Sincerely,

JAMES G. PRICE, M.D.
Associate Professor, Department of Family Practice.

Curriculum vitae enclosed.

CURRICULUM VITAE—JAMES G. PRICE, M.D.

Birth: 20 June 1926, Brush, Colorado, son of John H. Price, D.D.S. and Laurette Dodds Price.

Married: Janet Alice McSween of Brush, Colorado, 1949: Four children.

Education: Pre-Med.: University of Colorado, B.A., 1948; Medical School: University of Colorado, M.D., 1951; Internship: Denver General Hospital, Denver, Colorado; Certified as Diplomate, American Board of Family Practice, 1972. Recertified, 1977.

Academic Honors: Phi Delta Chi—National Chemistry Honorary, 1944; Phi Beta Kappa, 1948; Alpha Omega Alpha, 1950; Recipient, Silver and Gold Award for Outstanding Alumnus, Colorado University Alumni Association, 1975.

Military: USNR, 1944–46.

Local and State Medical Societies: Past President, Morgan County Medical Society; Colorado Medical Society Judicial Council—9 years; Colorado Blue Shield Advisory Committee—3 years; Colorado Academy of General Practice, President—1964, Board of Directors—7 years.

National Medical Activities: American Academy of Family Physicians—Commission on Membership and Credentials—3 years; Vice-speaker, Congress of Delegates—1967–68; Speaker, Congress of Delegates—1969–72; President-elect—1972–73; President—1973–74; Member of numerous committees of the Academy and its Board of Directors.

Past Professional Activities:

Advisory Board and Executive Committee, Intersociety Council for Heart Disease Resources (ICHD).

Board of Directors and Chairman, University of Colorado Development Fund, 1967–73.

Author of section on small hospitals, "The Medical Staff in the Modern Hospital," McGraw Hill, 1967.

Principle Speaker, 18th Annual Meeting of Directors of Cardiology, 1971.

Speaker, AMA Meeting, "The Quality of Life: The Middle Years."

Program Chairman, Family Health Foundation of America Conference on Primary Health Care, "A Time For Cooperative Effort," Washington, D.C., 1976.

Participant, Speaker or Chairman in multiple other meetings concerning Family Practice.

Associate Professor in Family Practice, University of Colorado, 1973–77.

Family Physician in Private Practice, 1952–78.

Current Activities:

Associate Professor in Family Practice, University of Kansas Medical Center, Kansas City, Kansas, 1978.

Board of Trustees, Family Health Foundation of America.

Board of Directors, American Board of Family Practice.

Chairman, Residency Review Committee for Family Practice, (member since 1971).

Author, Nationally syndicated newspaper column: "Your Family Physician."
Editorial Advisory Board, "Medical World News."
Medical Editor, "AAFP Home Study Self-Assessment Program."
Medical Consultant for Current Health.
PMA Commission on Sales Training Program.
Parliamentarian for AAFP Congress of Delegates, 1977–78.
President—American Board of Family Practice, 1979.

FARMINGTON, CONN., *January 31, 1979.*

Subject: Congressional action on Darvon.
Mr. LOWELL WEICKER,
Russell Senate Office Building, Washington, D.C.

DEAR SENATOR WEICKER: Would you please see that a copy of this letter (inclosed) gets to the proper Congressional committee people, if you yourself are not involved in the hearing on Darvon and if possible, let me know who they are. I am strongly opposed to removing Darvon from the market or even putting it on the dangerous drug list (which would mean a visit to the doctor every time the prescription was filled).

There is no truth to the statement of one of Ralph Nader's men that Darvon or one of its compounds is no more efficacious of relieving pain than aspirin.

I have been ill and in severe pain for the last four years and if it were not for Darvocet (Darvon and tylenol combined) would have had to take a more severe analgesic which would have been addictive. My husband is in 24-hours-a-day pain because of heart surgery and there is no drug on the market today that he could safely take except Darvon. For Mr. Nader to say that aspirin is just as good as Darvon is merely a theoretical statement by someone who has not been in pain year after year. I have noticed that after four years of being on Darvon, that the drug is not addictive, for when pain is not present because of my recovery, I simply forget to take the pills because they are not needed.

Even if the statistics were true and not slanted in an adverse direction, limiting the use of Darvon does not solve the problem for those people who are in constant pain—it would force them to addictive medication. I assume that there are a great many in pain caused by arthritis who would present the same argument I have put forward. My 80-year-old mother is one such person and taking Darvon out of reach of people like her would cause terrible hardship.

I can only conclude that Mr. Nader has launched this campaign wrecklessly without giving any thought to those people who need this drug, and would have second thoughts if he were one of the tens of thousands of peple who must live with pain every day of their lives. Mr. Nader's action is a reprehensible cheap try for publicity and I believe his statistics are faulty. He should look into statistics on how much relief this drug offers safely to suffering people. Please see that my arguments against banning or limiting the use of Darvon are heard by the necessary people. My husband concurs with the thoughts of this letter and so thanking you in advance, we are:

NORMAN R. TOFFOLON.
SHIRLEY I. TOFFLLON.

ELI LILLY & CO.,
Indianapolis, Ind., January 26, 1979.

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

DEAR SENATOR NELSON: As requested in your letter of January 15, 1979, to Mr. Richard D. Wood, I am enclosing responses to items one, two, three, and four. In addition to the enclosed response to item one, we are still compiling more published and unpublished information, which we will provide you promptly. The material supplied in response to item three is confidential commercial information which has not been publicly disclosed, and we respectfully request that the Committee preserve its confidentiality.

Sincerely yours,

EDGAR G. DAVIS, *Vice President Corporate Affairs.*

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

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

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

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

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

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

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

The foregoing information completes our response to question number 1.

Very truly yours,

EDGAR G. DAVIS,
Vice President, Corporate Affairs.

RESPONSE TO ITEM NO. 1

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

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

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

HUMAN PHARMACOLOGY

After the administration of a single dose of propoxyphene in man, plasma propoxyphene concentrations reach peak levels around 2 hours and decrease thereafter, with a half-life of 6 to 12 hours. Peak plasma concentrations of norpropoxyphene are noted within a half to one hour following peak propoxyphene concentrations. The half-life of norpropoxyphene is 30 to 36 hours.

In human subjects given a loading dose of propoxyphene (300 mg napsylate [N] or 195 mg hydrochloride [HCl]) followed by 100 mg N or 65 mg HCl at four-hour intervals for 31 doses (5 days), peak plasma concentrations of norpropoxyphene between 1.0 and 1.2 micrograms/ml (with the hydrochloride) and between 0.75 and 1.0 micrograms/ml (with the napsylate) were noted at about 120 hours.

Single daily doses of 125 mg norpropoxyphene administered to humans for 7 days resulted in peak plasma concentrations of norpropoxyphene of 0.25 to 0.55 micrograms/ml and did not elicit any overt adverse effect.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In acute toxicity studies the oral LD_{50} values for propoxyphene HCl in mouse, rat, and dog are 282, 230, and 100 mg/kg, respectively, and are approximately equivalent to 35, 29, and 12 times the maximum recommended dose of 8 mg/kg/day for humans. Propoxyphene napsylate in acute doses is about one-half as toxic as the hydrochloride salt, especially in dogs, due to the more gradual absorption of the napsylate salt. Animals given lethal doses of propoxyphene die following clonic and tonic convulsions.

Acute toxicity studies in rodents reveal that the LD_{50} for propoxyphene is lower than that for norpropoxyphene, and in the rat this difference is of the order 4 to 5 times (on a molecular basis). The acute lethality of norpropoxyphene in mice is not reduced by naloxone.

Dogs tolerated large daily oral doses of either the hydrochloride or napsylate salt of propoxyphene (equivalent to 35–70 times the maximal human dose) for as long as two years. In a few dogs some fatty change, usually of slight degree, was noted in the liver.

The oral administration in dogs of increasing doses of propoxyphene, beginning with 20 mg/kg/day and increasing to 60 mg/kg/day in 5 to 15 mg/kg increments at intervals of three to four days over a period of 17 days, resulted in maximal plasma norpropoxyphene concentrations of 16–20 micrograms/ml, at which time propoxyphene concentrations were 2 to 3 micrograms/ml. (It should be recalled that the starting dose of 20 mg/kg/day is 2½ times the recommended human dose.) The dogs remained ambulatory on this enormous dosage regimen, free of any evidence of circulatory impairment, although they lost weight due to anorexia and occasional emesis, noted usually only after the first incremental dose, along with sedation and tremor. Tissue analyses for propoxyphene and norpropoxyphene indicated higher concentrations in plasma than in the following tissues: brain, heart, kidney, liver, lung. Highest concentrations of both compounds were observed in the liver. Slightly increased serum glutamate pyruvate transaminase and alkaline phosphatase values were observed, but glucose, bilirubin, creatinine, or BUN remained unchanged.

Animal studies indicate that norpropoxyphene has little analgesic ("opioid") property (½ to 1/40 that of propoxyphene, depending on the assay method utilized), while its local anesthetic properties are two to three times that of the parent compound. Opiate effects are antagonized by naloxone, nalorphine, and levallorphan, whereas local anesthetic effects are not.

The toxicological effects of propoxyphene relate to its analgesic (opioid) properties, which are shared to a much lesser degree by norpropoxyphene, and are readily reversed by antagonists such as naloxone. The local anesthetic properties, shared by both propoxyphene and norpropoxyphene, but to a greater extent by norpropoxyphene, lack specific antagonists. Since (1) both propoxyphene and norpropoxyphene possess local anesthetic effects not reversible by specific antagonists and (2) in view of the higher plasma and tissue concentrations of norpropoxyphene attained during chronic propoxyphene administration, as well as (3) the relatively long half-life of norpropoxyphene, the possible role of the local anesthetic properties of the parent compound and its principal metabolite in propoxyphene-induced toxicity merits further study.

The local anesthetic effects of norpropoxyphene have been compared with standard local anesthetic agents ,such as dibucaine, cocaine, and lidocaine, by

measurement of inhibition of cervical-sympathetic nerve action potential amplitude in the rat (Nickander, R., J. Pharm. & Exper. Ther., *200*:245–253, 1977). Dibucaine was the most potent local anesthetic tested, while lidocaine was the least potent. Norpropoxyphene was more potent than propoxyphene, and both were more potent than cocaine in this system.

Compounds possessing local anesthetic activity also modify cardiac conduction. Since electrocardiographic changes have been reported in some cases of propoxyphene overdosage in humans, the possibility arises that the local anesthetic effect of norpropoxyphene (and propoxyphene) might contribute to the toxicity or lethality of propoxyphene overdose, by a deleterious effect on cardiac conducting tissue.

The effects of propoxyphene and of norpropoxyhene on cardiac conduction have been studied *in vivo* and *in vitro* (Holland and Steinberg, Toxicol. & Appl. Pharm., *47*:161–171, 1979. Propoxyphene and norpropoxyphene, 10^{-6} to 10^{-4} molar, (0.34–34 μg/ml) decreased Vmax,[1] action potential duration, and cellular refractorIness of isolated canine Purkinje fibers *in vitro*. Norpropoxyphene was more potent with respect to reduction of Vmax, while the shortening of the action potential duration (at 95% repolarization) was similar for both propoxyphene and norpropoxyphene. The decrease in the effective refractory period by either compound was approximately equivalent, and thus the ratio of effective refractory period to action potential duration was essentially unaltered by either compound.

Both propoxyphene and norpropoxyphene have negative inotropic and chronotropic effects on guinea pig atria *in vitro*. Atrial rate of contraction (ED_{50}) was slowed 50 percent by propoxyphene $3.5/1.3\times10^{-5}$M (11.7/4 μg/ml) and by norpropoxyphene $5.6/1.6\times10^{-5}$M (18.7/5.3 μg/ml). Atrial tension development was decreased by 50% in the presence of $1.40/01.01\times10^{-4}$ (46.7/0.3 μg/ml) propoxyphene or $7.9/2.0\times10^{-5}$ (26.3/6.7 μg/ml) norpropoxyphene. Thus, propoxyphene had a slightly greater negative chronotropic effect and a lesser negative inotropic effects.

Amsterdam et al. (Clin. Res., *25*:A204. 1977) observed a decrease in tension developed *in vitro* by cat right ventricular papillary muscle with either propoxyphene or norpropoxyphene at 10^{-4} molar (34 μg/ml). After washout, tension was promptly restored with isoproterenol. Neither propoxyphene nor norpropoxyphene altered the time to peak tension of the contracting muscle.

Lund-Jacobson (Acta Pharmacol. & Toxicol., *42*:171178, 1978) compared the effects of infusions of equimolar doses of propoxyphene and norpropoxyphene on the ECG in conscious rabbits. Prolongation of QRS, intermitted A–V block and ventricular extrasystoles were observed during both propoxyphene and norpropoxyphene infusion. The ECG changes were determined to be independent of respiratory depression and were viewed as resembling those seen in quinidine intoxication. The QRS prolongation correlated with plasma concentrations of propoxyphene and norpropoxyphene, although direct time comparisons were not made.

The effects of propoxyphene and norpropoxyphene infusions 0.72 to 7.2 μg/kg were studied in unanesthetized dogs. (Signs of centeral nervous system toxicity appeared in all dogs receiving the 7.2 μg/kg infusion of propoxyphene.) The effects of the 7.2 μg/kg doses of propoxyphene and norpropoxyphene on the P–R interval (atrioventricular conduction time) were similar, i.e., it was increased about 35 milliseconds. Plasma propoxyphene concentrations during the infusion of 7.2 μg/kg were 3.5/0.4 μg/ml. Plasma concentrations of norpropoxyphene were one-fourth those of propoxyphene.

When the lower doses of propoxyphene were infused, heart rate diminished, while the 7.2 μg/kg dose increased the heart rate about 25 beats per minute. Norpropoxyphene at the high dose increased heart rate less markedly, that is, about 16 beats per minute. The QT_c[2] increased slightly with increasing doses of propoxyphene, and the QRS duration was not significantly increased.

His bundle conduction, A–H and H–V intervals, were prolonged by both propoxyphene and norpropoxyphene. Norpropoxyphene was significantly more potent in prolonging H–V intervals than propoxyphene.

If the infusion of either propoxyphene or norproxyphene was increased beyond 7.3 μg/kg to a total of 16.3 μg/kg, second degree A-V nodal block usually appeared.

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[1] Maximum rate of rise of the action potential.
[2] QT_c = QT interval divided by (R-R interval).

CLINICAL REPORTS

Since it has been suggested that the negative inotropic and dromotropic effects attributable to the local anesthetic effects of propoxyphene and norpropoxyphene may play a role, in certain cases, in the demise of individuals consuming excessive amounts of propoxyphene, case reports wherein cardiac abnormalities were reported in association with propoxyphene overdose are reviewed below.

In 1964 McCarthy and Kennan (J.A.M.A., *187*:164–165, 1964) published one of the first reports of fatal propoxyphene overdose. A 15-year-old girl took 1280 mg propoxyphene hydrochloride with suicidal intent. When she arrived at the emergency room she was comatose and cyanotic with shallow respiration. Persistent generalized convulsions began almost immediately, and succinylcholine chloride was given intravenously in an effort to relax the respiratory muscles so that artificial ventilation could be established. Cardiac arrest occurred at this point. An endotracheal tube was inserted, and artificial ventilation and external cardiac massage immediately begun. Nalorphine and levarterenol were administered intravenously. Shortly thereafter blood pressure was noted at 90/40 mm Hg, pulse 120 per minute. The patient remained deeply comatose with continued convulsive seizures separated by periods of apnea. Intravenous and intramuscular diphenylhydantoin and intravenous paraldehyde were administered to control convulsions. Peritoneal dialysis was begun, during which a bigeminal cardiac rhythm was noted that "responded well to intravenous procaine amide hydrochloride" (an antiarrhythmic agent with local anesthetic properties). The patient's course was slowly downhill, complicated by electrolyte imbalance and infection, and she expired 5 days later. Autopsy revealed cerebral edema, atelectasis, focal pneumonia, pleural effusion, and necrosis of the brain. The authors ascribed the episode of cardiac arrest to the severe hypoxia. They also observed that the bigeminal rhythm was easily controlled with procaine amide and that this rhythm disturbance had been noted previously and should be considered in the management of such patients.

Comment: The cardiac arrest and bigemial rhythm almost certainly were engendered by the severe anoxia and cyanosis (and the acidosis that undoubtedly developed). It would seem unlikely that the bigeminal rhythm was caused by the local anesthetic effects of propoxyphene or norpropoxyphene inasmuch as the abnormal rhythm was reported to have responded well to intravenous procaine amide, itself a local anesthetic.

Qureshi (J.A.M.A., *188*:470–471, 1964) reported cardiac and other findings in an 18-year-old woman who ingested 832 mg propoxyphene hydrochloride at one time in a suicidal attempt. She promptly became disoriented and had generalized convulsions followed by cyanosis, coma, and circulatory shock. At examination, heart rate was 110, and apical systolic murmur, respirations slow and shallow with cyanosis. More convulsions, coma, and deep cyanosis followed. ECG revealed sinus tachycardia, nonspecific ST–T changes, and QRS 0.2 seconds, suggestive of intraventricular conduction delay. Appropriate measures were taken to counteract CNS depression and shock, and the patient improved and was discharged after an uneventful course, apparently well, three days later. With clinical improvement the ECG returned to normal.

Comment: In his commentary the author notes that "the cardiac findings in this case may have been due to a direct toxic effect of propoxyphene on the heart; however, the possibility that these cardiac manifestations may have been due to myocardial hypoxia associated with the respiratory depression cannot be excluded."

Sigurd and Jensen (Danish Med. Bull. *18*:166–168, 1971) reported a case of propoxyphene poisoning "complicated by circulatory arrest caused by asystole followed by reversible heart pump failure." The patient was a 45-year-old man without known heart disease who was jailed because of public drunkenness only to be discovered 9½ hours later to be comatose. It was determined later that he had taken a barbiturate and propoxyphene, in addition to alcohol, in an attempt to commit suicide. On admission he was cyanotic and deeply comatose. Cyanosis rapidly became severe, and cardiac arrest occurred; an ECG at that time revealed no cardiac electrical activity. Cardiopulmonary resuscitation measures were undertaken, including intravenous bicarbonate solution and adrenalin I.V. and intracardially. The ECG then revealed widened QRS and absent P waves, rate 80 per minute, no perceptible pulse. A solution of isoprenaline in isotonic glucose was infused, and the ECG then showed less-widened

QRS, absent P waves, rate 150, and a "well filled pulse." The patient continued to improve slowly (BP 130/80 mm Hg on second day), but he remained unconscious during the first two days, without convulsions. The ECG subsequently revealed "tall double-peaker P waves" which remained unchanged during the nine days he was on the ward. At no time were signs of myocardial ischemia seen in the ECG and no rise occurred in serum lactate dehydrogenase.

His hospital course was complicated by a psychosis and transient renal functional impairment in association with a mild diabetes insipidus-like syndrome, possibly as a result of the anti-ADH effect of propoxyphene. (Bower et al., Proc. Soc. Exp. Biol. and Med., *120*:155–157, 1965; McCarthy and Keenan, *vide supra*).

Propoxyphene was detected in the urine by thin layer chromatography, and serum barbiturate was 0.3 mg% (as aprobarbitate, W.H.O.). No plasma electrolyte data are included in the report.

Comment: The patient ingested three CNS-depressant agents in attempting suicide and was not seen medically for 10 hours or more. He was comatose and cyanotic, and cardiac arrest occurred within moments following admission. Undoubtedly the myocardium had sustained injury during the long interval of coma and anoxia. Acidosis was treated promptly, and cardiopulmonary resuscitation ultimately saved his life. There were many factors, obviously, contributing to myocardial ischemia and injury (cardiac arrest persisted 8 minutes). The role, if any, of the local anesthetic effects of propoxyphene and norpropoxyphene in the disturbance of cardiac function in this patient can only be surmised.

The serial electrocardiograms presented in this report suggest the presence of hyperkalemia. The infusion of glucose and the intravenous bicarbonate that the patient received would have tended to improve the ECG. Any hyponatremia accompanying the mild diabetes insipidus syndrome that developed would enhance any electrocardiographic manifestation of hyperkalemia.

Gustafson and Gustafson (Acta Med. Scand., *200*:241–248, 1976) reviewed pertinent laboratory and clinical findings in eleven cases (10 patients, one of whom was admitted twice) of propoxyphene overdose observed at University hospital in Lund, Sweden. None had ingested propoxyphene alone (5 had ingested one or more additional CNS-depressant drugs). In addition, alcohol intake was reported in six.

The principal clinical findings consisted of (1) coma (six patients were in deep coma on admission, four of whom had taken tablets containing barbiturate and one a phenothiazine preparation), (2) depressed respiration, 15/minute or less, in 7 cases (two patients were apneic and severely acidotic and required a mechanical respirator), (3) circulatory abnormalities, (4) metabolic acidosis, (5) convulsions. (The absence of any mention of cyanosis is curious in view of the presence of respiratory depression and periods of apnea.)

With respect to cardiovascular function: One patient on first admission had a systolic blood pressure of 80 mm Hg. On second admission he manifested circulatory arrest (ventricular fibrillation) associated with severe acidosis. Sinus tachycardia was present on admission in five patients, and in the remaining cases the heart rate was normal. The ECG revealed QRS widening in four patients (two of whom had severe acidosis), and in one patient a bundle branch block was noted on admission that was present at discharge 33 hours later, suggesting the prior existence of this conduction defect.

Acidosis was noted in four patients (one of whom was admitted with acidosis on two occasions). Convulsions were noted in only one patient, and severe acidosis was present in this patient.

The two patients with severe acidosis merit additional discussion. One was a 21-year-old man who was first admitted (case 1) comatose after excessive ingestion of alcohol and a propoxyphene-barbiturate-aspirin preparation. Systolic blood presure was 80 mm Hg, but there were no signs of respiratory depression. He recovered over a 20-hour period, uneventfully. However, he was admitted again (case 5) 8 months later, again having imbided heavily and having taken 650 mg propoxyphene, 3.5 gm aspirin, and 500 mg vinbarbital. On admission he was pulseless and apneic. Defibrillation was successful, and intracardiac adrenalin and intravenous isoprenaline were administered. At this time the ECG revealed widened QRS (0.14 seconds), but an hour later the ECG showed sinus rhythm and normal QRS. Mechanical respiration was continued, and a metaraminol drip established to maintain blood pressure. However, his cardiac function ceased 15 hours later. Plasma propoxyphene concentration on admission was 0.74 micrograms/ml, norpropoxyphene 0.39 micrograms/ml.

The second patient (case 7) was a 16-year-old girl who, after drinking alcohol, attempted suicide by ingesting about 4.5 grams of propoxyphene. She convulsed shortly thereafter and on admission one hour later was comatose and apneic. She was severely acidotic. Systolic blood pressure was 100 mm Hg, and the ECG revealed sinus tachycardia, widened QRS (0.12 seconds), and prominent S waves (except in lead III). Mechanical respiration was instituted, and subsequent seizures were controlled with intravenous diazepam. She responded well to treatment, acidosis subsided, and the ECG was normal in six hours. She was discharged after two days. Her plasma propoxyphene concentration was 0.51 micrograms/ml; and her norpropoxyphene concentration, 0.79 micrograms/ml, 2.5 to 3 hours after ingestion.

Propoxyphene and norpropoxyphene analyses were carried out utilizing the gas chromatograph-mass spectrometer technique of Wolen (Toxicol. Appl. Pharmacol, *19*:480, 1971). Highest plasma concentrations were found in the fatal case; and the patient with the second-highest concentration, over 0.5 micrograms/ml, had very severe symptoms. In discussing the clinical symptomatology the authors note that cardiac arrest may occur secondary to respiratory depression and apnea and that QRS widening and ventricular bigeminy have been observed in humans taking excessive doses of propoxyphene.

Comment: The development of respiratory depression and apnea, when excessive propoxyphene has been ingested either alone or with CNS-depressant agents, results in severe anoxia and acidosis. While the use of a narcotic antagonist to reverse the opiate-indicated respiratory depression is of prime importance, the need to correct acidosis needs emphasis. Acidosis depresses myocardial contractility, diminishes cardiac responsiveness to catecholamines, and predisposes to ventricular fibrillation. The importance of correcting acidosis under conditions of anoxia with acute cardiopulmonary failure cannot be overemphasized. The use of intravenous sodium bicarbonate in cardiopulmonary resuscitation is described in *The Heart*, J. Willis Hurst, Ed., 4th Edition, 1978, McGraw Hill, New York.

FINKLE STUDY

In a review of 1,022 medical examiner cases associated with propoxyphene overdose, Finkle *et al.* (J. Forensic Sci., *21*:706–742, 1976) observed a small group of cases exhibiting a common pattern of symptoms prior to death, the most striking of which was a survival time of 15 minutes or less, that is, "sudden death." He examined various toxicologic and epidemiologic aspects in 52 cases, in all of which death apparently occurred within 15 minutes (interval from time last seen alive until death) of unexplained cause or causes.

Age and sex distributions differed from those observed for the total study population, inasmuch as the greatest proportion of males was noted in the 21–25 and 46–50 age groups. Body weights were not remarkable. In 4 of the 10 cases for which there was a medical history, "a heart condition" was noted. Single instances of hypertension, asthma, epilepsy, paraplegia, ulcers, and "recent head injury" were also noted. The drug abuse histories were noteworthy in that 44% had a documented history of abusing some substance (34% for total study group). Respiratory arrest, the predominant symptom (85%), was almost twice as frequent. Seizure frequencies were about the same. Coma was observed less frequently (15% vo. 40%), but this may be due to the brief survival. The authors concluded that "the final collapse is centrally mediated and rarely cardiovascular."

There was a very high incidence of the use of other drugs in these "sudden death" cases; 85 percent had some other drug in addition to propoxyphene, in contrast to 76 percent for all cases. In the sudden death group, 52 percent had alcohol involved, in contrast to 42 percent in the total group. The other drugs, determined by case investigation or by chemical analysis, were predominantly central nervous system depressants. In 40 percent of the cases, concentrations of drug (by laboratory analysis), other than propoxyphene or alcohol, were significantly high in and of themselves. Diazepam was the most frequent. The data indicate that alcohol and other drugs played a major role in these cases. The particular importance of alcohol in the sudden death cases is attested to by the fact that blood alcohol concentrations were predominantly associated with lower propoxyphene concentrations. In 75 percent of the sudden death cases associated with alcohol, plasma propoxyphene concentrations were less than 2.5 micrograms/ml., whereas in the total study group 72 percent of the sudden death cases associated with alcohol had values less than 7.0 micrograms/ml.

TENNANT STUDY

Propoxyphene napsylate has been evaluated by Tennant (J. Natl. Med. Assn., *66*:23–27, 1974; J.A.M.A., *232*:1019–1022, 1975) for heroin detoxification and maintenance. Under double-blind conditions, 29 adults were admitted to a 180-day maintenance program. About ¼ of the patients remained in the study more than 90 days; a few remained for as long as two years. The maximum daily dose of propoxyphene napsylate was 1200 mg, starting with 400 mg per day. Patients who received a single dose of 600 mg reported short-term dysphoria, but otherwise no serious toxic effects were noted. Electrocardiograms, chest X-ray, and electroencephalograms were evaluated before and at the third and sixth month of the study. The ECG tracings were reviewed by a cardiologist and no changes were observed, nor were changes observed in the other examinations.

ECG MONITORING

The electrocardiographic effects of propoxyphene were observed in two male volunteers, ages 56 and 60, admitted for study to the Lilly Clinic, Wishard Memorial Hospital, Indianapolis. The twenty-four-hour ECG was recorded for each subject, using Holter monitors. After a six-day control period, a single 300 mg dose of propoxyphene napsylate was given, and blood stamples were obtained at various intervals over the next 48 hours. Maximum concentrations of propoxyphene and norpropoxyphene observed in these two subjects were 0.25 and 0.37 (propoxyphene) and 1.1 and 1.4 (norpropoxyphene) micrograms/ml, respectively. From day 9 through day 15 the subjects received propoxyphene napsylate 10 mg every 4 hours (i.e., 600 mg/day). Day 16 through day 25 served as the posttreatment control period. Neither subject manifested any change in P–R, QRS, or QT_c during the period of propoxyphene administration, in comparison with pretreatment or posttreatment control tracings. Ventricular premature beats were observed slightly more frequently in one subject during treatment, while a slight decrease in ectopy was noted in the other. Neither change is significant.

GENERAL COMMENT

Bigeminal cardiac rhythm has been described relatively frequently in cases of propoxyphene overdose, and it is of some interest to note that in the case reported by McCarthy and Keenan "a bigeminal rhythm developed but it responded well to intravenously administered procaine amide hydrochloride"—an antiarrhythmic agent with potent local anesthetic effects.

Serial ECG tracings in heroin addicts on propoxyphene napsylate detoxification-maintenance programs involving large doses of propoxyphene for periods of many weeks to several months do not indicate any effects on conduction or other aspects of cardiac electrophysiology. Twenty-four-hour Holter ECG monitoring of volunteers on usual therapeutic doses of propoxyphene for several days yields no indication of any effect of propoxyphene on cardiac conduction or function.

The possibility that norpropoxyphene cardiotoxicity plays a role in propoxyphene toxicity merits further study. Certainly there are measurable, although relatively minor, effects on myocardial conduction, demonstrable by *in vitro* and *in vivo* animal experiments. Reports of human toxicity that provide cardiac and electrocardiographic commentary strongly suggest that cardiocirculatory problems—such as cardiac arrest, ventricular fibrillation, and arrhythmias—arise mainly from severe anoxia, due to respiratory depression and apnea, acidosis, which may be severe, and electrolyte imbalance. Central nervous system depression *per se* may directly interfere with cardiopulmonary and circulatory function. The impression is gained that prompt correction of acidosis has not received the therapeutic attention that it merits. Management of any cardiac dysfunction in these cases would be greatly enhanced by correction of acidosis.

While the local anesthetic effects of nonpropoxyphene on cardiac conduction might assume somewhat greater significance in an individual severely toxic from drug overdose, the major threats to adequate cardiac function in this situation remain, namely, anoxia and acidosis and, later on, electrolyte imbalance.

RESPONSE TO ITEM NO. 2

Sales volume of Lilly propoxyphene in major population areas, and the dollar volume of sales of Lilly propoxyphene per unit of population in the 24 Standard Metropolitan Statistical Areas comprising the DAWN system.

Following is information relative to the sales of Lilly propoxyphene in the 24 Standard Metropolitan Statistical Areas comprosing the Dawn system which are also the major population areas in the United States. It must be understood that Lilly products, including Darvon, are sold through approximately 400 service wholesale drug distributors. Lilly does not sell its products directly to community pharmacies or hospitals.

The attached table reflects Lilly dollar sales of its propoxyphene to wholesalers located within the geographic boundaries of each of the 24 SMSA's.

Since the pharmaceutical market is highly competitive, wholesalers located within a specific SMSA sell and distribute Lilly products outside the boundaries of the SMSA in which they are located. Conversely, wholesalers located outside sell and distribute Lilly products inside the SMSA.

In addition to the movement of merchandise across SMSA boundaries in both directions, people move across these boundaries also. In our highly mobile society, some people who live within the boundaries may work and purchase goods and services outside the area and some who live outside may work and purchase goods inside.

Therefore, because of the movement of both merchandise and people in and out of the areas, the sales reflected in the table should not be relied upon to be indicative of the availability or consumption of Lilly's propoxyphene within the SMSA.

LILLY SALES OF PROPOXYPHENE TO WHOLESALERS LOCATED IN STANDARD METROPOLITAN STATISTICAL AREA (SMSA)

[In thousands]

SMSA	Sales	
	1977	1978
Atlanta	$593	$1,791
Buffalo	548	545
Denver	943	1,078
Minneapolis-St. Paul	843	858
San Antonio	356	396
Boston	1,216	1,448
Chicago	1,455	1,282
Dallas	731	824
Washington, D.C	917	1,177
Indianapolis	514	363
Cleveland	1,495	1,768
Miami	575	553
Norfolk	232	249
Los Angeles	1,716	2,146
New York	2,957	2,737
Detroit	2,584	3,017
Kansas City	1,471	1,608
New Orleans	922	830
Oklahoma City	854	783
Philadelphia	1,865	1,721
Phoenix	461	466
San Diego	362	438
San Francisco	612	619
Seattle	290	381

Response to Item No. 3

Advertising and Promotion Expenses for Lilly Propoxyphene

(Figures deleted at request of Eli Lilly and Co.)

Note: Advertising and promotional expenditures include such expenses as samples, product literature, journal advertising, direct mail, exhibits and visual aids. Company records for the information requested are no longer available for the years 1957 through 1969.

Response to Item No. 4

Propoxyphene was initially classified by the World Health Organizaiton (WHO), in a document actually published in March, 1956, as a dependence-producing substance (Exhibit A, pages 9 and 10 retyped) based on chemical

structure, pharmacologic data, and the preliminary impressions of Dr. Nathan B. Eddy (Exhibit B). Since the United States was obligated by international agreement to implement the WHO recommendation, the United States Treasury Department published February 29, 1956, a proposed rule in the Federal Register seeking to declare propoxyphene, among other drugs, an addiction-forming or an addiction-sustaining drug, similar to morphine and that it was an opiate (Exhibit C). A hearing was held May 3, 1956, by the Treasury Department, Bureau of Narcotics in which Eli Lilly and Company presented evidence which indicated there was no evidence to sustain a conclusion that propoxyphene possessed addiction-producing or addiction-sustaining qualities similar to morphine (transcript available). The new drug application for propoxyphene was approved September 9, 1957, and marketing began in the fall of 1957. In March of 1962, the Treasury Department, Bureau of Narcotics published in the *Federal Register* its determination that propoxyphene was not an opiate (Exhibit D). Following this determination, the WHO in 1964 withdrew its initial evaluation on the basis of five years of experience, repeated observations of the use of propoxyphene, and the United States determination (Exhibit E, pages 5 and 8). WHO reaffirmed that controls on propoxyphene were unnecessary in 1969 and 1970. The WHO Scientific Group reported in 1972 that dependence liability and frequently of nonmedical use of propoxyphene was low.

EXHIBIT A

(Note.—Exhibit A, an article entitled "Expert Committee on Drugs Liable to Produce Addiction," has been omitted because of its poor readability. Relevant parts of pages 9 and 10 have been re-typed and appear below.)

WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES No. 102—EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION, SIXTH REPORT, MARCH 1956

5.2.2 4-DIMETHYLAMINO-1,2-DIPHENYL-3-METHYL-2-PROPIONOXYBUTANE

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane, because it (1) will only partially suppress the abstinence phenomena of a known morphine addiction, and (2) will in part sustain a morphine addiction, must be considered as having no greater addiction liability than codeine, and that 4-dimethylamino-3-1,2-diphenyl-3-methyl-2-propionoxybutane and its salts are assimilable to the drugs mentioned in Group II of the 1931 Convention. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction:

Recommends that its opinion with respect to 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane and its salts be communicated to the Secretary-General of the United Nations.

UNITED STATES NOTIFICATION WITH RESPECT TO NINE NEW SYNTHETIC DRUGS

Pursuant to Paragraph 1 of Article 1 of the Protocol signed at Paris on 19 November 1948, bringing under international control drugs outside the scope of the Convention of 13 July 1931, as amended by the Protocol signed at Lake Success on 11 December 1946, the United States Government presents a notification that the following named drugs, and their respective salts, all of which are or may be used for medical or scientific purposes and to which the Convention of 13 July 1931 does not apply, are considered liable to the same kind of abuse and productive of the same kind of harmful effects as the drugs specified in Article 1, Paragraph 2, of the said Convention:

Ethyl-2,2-diphenyl-4-morpholinobutyrate
4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxy butane
1,3-Dimethyl-4-phenyl-4-propionoxyhexamethyleneimine
4-Carbethoxy-1-methyl-4-phenylhexamethyleneimine
4-Carbethoxy-1,3-dimethyl-4-phenylhexamethyleneimine
4-Carbmethoxy-1,2-dimethyl-4-phenylhexamethyleneimine
3-Hydroxy-N-phenethylmorphinan
1-[2-(p-aminophenyl)-3thyl]-4-carbethoxy-4-phenylpiperidine
4-Carbethoxy-1-(2-hydroxy-2-phenyl-ethyl)-4-phenylpiperidine

This notification is respectfully submitted for appropriate decision as to the status of the new drugs and of their respective salts under the Convention of 13 July 1931, as amended by the Protocol of 1946.

Suggestion for an international nonproprietary name for each of the above-named drugs will be submitted at a later date.

EXHIBIT B

(This letter is from Mr. Anslinger, U.S. Commissioner of Narcotics to WHO. Dr. Eddy's study is attached.)

There are enclosed two copies of reports on the above-named drugs (identified as Enclosures A to E respectively) submitted by Dr. Nathan B. Eddy of the National Institutes of Health, United States Public Health Service, Bethesda, Maryland, U.S.A.

H. J. ANSLINGER,
U.S. Commissioner of Narcotics,
Representative of the United States on
the Commission on Narcotic Drugs of the
United Nations.

Enclosures.

ADDICTION LIABILITY OF ALPHA-4-DIMETHYLAMINO-1,2-DIPHENYL-3-METHYL-4-PROPIONYLOXYBUTANE (LILLY 16298, PROPOXYPHENE)

A. EFFECTS OF SINGLE DOSES IN NONADDICTED PATIENTS

Since this drug is very irritating, only the oral route was used. The compound was administered in single doses to 13 nontolerant former addicts in doses ranging betwen 50 to 400 mg. Table I shows the results of 25 trials. It is evident that this compound is fairly inert. Even the two subjects who were given a dose of 200 mg. at 8:30 a.m. followed by 400 mg. at 9:00 a.m., said "It is like water," although both complained of a slight headache. One subject who received 150 mg. one week and 200 mg. the following week, complained of diarrhea on both occasions.

B. SUPPRESSION OF SYMPTOMS OF ABSTINENCE FROM MORPHINE

Eleven subjects who had been stabilized in 240–280 mg. of morphine daily were given a total dose of 1200 mg. of No. 16298 during the first 24 hours after abrupt withdrawal of morphine. The drug was administered orally, in doses of 200 mg. at intervals of four hours, except at night when the interval was six hours. In a similar study using the same patients, the dose was increased to a total of 2400 mg. given in divided doses of 400 mg. In a control experiment, the same subjects were given placebo capsules which resembled the No. 16298 capsules on a comparable schedule.

In a positive control experiment, nine of these 11 subjects were given morphine injections on a four-hour schedule and they were informed only that another compound was being tested. The results of this experiment with the 400 mg. dose of No. 16298 (2400 mg. in 24 hours) are illustrated in Figure 1. Intensity of abstinence was reasusred by the Himmelsbach scoring system, beginning at the 14th hour of abstinence and continuing at hourly intervals to the 24th hour. The figure illustrates that when morphine was given the score fluctuated between 3 to 8 points. When placebo injections were given instead of morphine the intensity of abstinence rose to 30 points at the end of 24 hours. When No. 16298 was administered in doses of 400 mg., every four hours, the intensity of abstinence was significantly reduced beginning with the 14th hour and continuing through the 24th hour. Two of 9 subjects to whom this dose was given showed excessive sedation and a depressed respiration of Cheyne-Stokes type. It was necessary to reduce the dose to 200 mg. twice for one patient and once for the other patient. Although all the other patients who received this high dosage showed depressed respiration, it did not become sufficiently serious to warrant discontinuation of the experiment. With the 200 mg. dose (total 1200 mg.) the abstinence scores from the 14th through the 24th hour were as follows: 14, 13, 14, 15, 16, 17, 18, 20, 20, and 23. These scores are very similar to those obtained with a 400 mg. dose except at the 14, 15, and 16th hour of abstinence. With the small dose, there was no serious depression of respiration but definite sedative effects were present.

All of the patients in whom No. 16298 was substituted stated that it was beneficial in that they slept more and were less nervous than they had been when no medication was given. None of them stated, however, that the effect of the com-

pound resembled that of a narcotic drug and none experienced a morphine-like "euphoria" at any time during substitution of No. 16298.

C. SUMMARY AND CONCLUSION

1. In doses ranging up to 400 mg. orally compound No. 16298 did not induce symptoms of morphine-like "euphoria" or behavior resembling that seen after administration of morphine in nontolerant former opiate addicts.

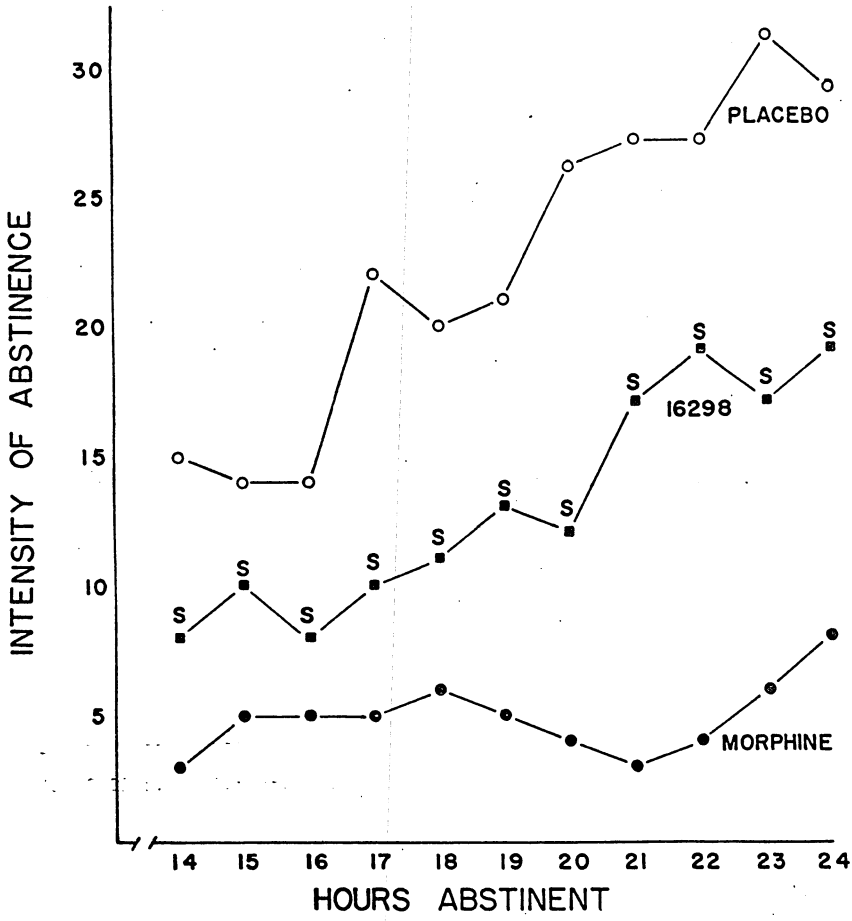
2. In doses of 200 and 400 mg. administered at intervals of approximately four hours, compound No. 16298 significantly suppressed the intensity of abstinence from morphine. The slight difference in the degree of depression by doses of 400 mg. as compared with doses of 200 mg. suggests that this drug would be incapable of completely suppressing symptoms of abstinence from morphine. When administered in repeated doses of 400 mg. during substitution tests definite sedative and, in some subjects, pronounced respiratory depressant effects were observed.

3. *Conclusion.*—Compound No. 16298 has addiction liability, as indicated by its ability to suppress signs of abstinence from morphine. However, its overall addiction liability is estimated to be no greater and is probably less than that of codeine.

TABLE 1.—SINGLE DOSES OF COMPOUND 16298 ORALLY

Dose (milligrams)	Number of subjects	Response
50	6	Negative.
100	2	Do.
150	5	Negative except 1 subject; diarrhea.
200	5	2 subjects slightly drowsy; 1 diarrhea.
250	5	1 subject slightly dizzy.
200 plus 400 [1]	2	Both complained of a light headache, but both sold, "It is like water."

[1] 200 mg were given at 8:30 a.m. and 400 mg additional were given at 9 a.m. For practical purposes the total dose was 600 mg.



The letter S signifies that this point is statistically significant as compared to a corresponding point for a placebo.

EXHIBIT C—PROPOSED RULE MAKING

DEPARTMENT OF THE TREASURY, BUREAU OF NARCOTICS

[21 CFR Ch. 11]

PIPERIDYL METHADONE, AND OTHER DRUGS

NOTICE OF PROPOSED RULE MAKING

Notice is hereby given, pursuant to the provisions of section 1 of the act of March 8, 1946 (60 Stat. 38; 26 U.S.C. 4731), section 4 of the Administrative Procedure Act (60 Stat. 238; 5 U.S.C. 1003), and by virtue of the authority vested in me by the Secretary of the Treasury (12 F.R. 1480), that a determination is proposed to be made that each of the following-named drugs has an addiction-forming or addiction-sustaining liability similar to morphine and is an opiate:

(1) 4.4-diphenyl-6-piperidine-3-heptanone (piperidyl methadone).

(2) Isopropyl 1-methyl-4-phenylpiperidine-4-carboxylate.

(3) 3-diethylamino-1.1-di(2-thienyl)utene (diethylthiambutene).
(4) 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine.
(5) 3-hydroxy-N-phenethylmorphinan.
(6) Ethyl 2,2-diphenyl-4-morpholinobutyrate.
(7) 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane.
(8) Ethyl 1-[2-(p-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylate.

Consideration will be given to any written data, views, or arguments, pertaining to the addiction-forming or addiction-sustaining liability of each of the above-named drugs, which are received by the Commisisoner of Narcotics prior to March 29, 1956. Any person desiring to be heard on the addiction-forming or addiction-sustaining liability of any of the above-named drugs will be accorded the opportunity at a hearing in the office of the Commissioner of Narcotics, 1300 E Street, NW., Washington 25 ,D.C., at 10:00 a.m. March 29, 1956, provided that each person furnishes written notice of his desire to be heard, to the Commissioner of Narcotics, Washington 25, D.C., not later than 20 days from the publication of this notice in the Federal Register. If no written notice of a desire to be heard shall be received within 20 days from the date of publication of this notice in the Federal Register, no hearing shall be held, but the Commissioner of Narcotics shall proceed to make a recommendation to the Secretary of the Treasury for a finding under section 1 of the act of March 8, 1946.

(60 Stat. 38; 26 U.S.C. 4731)

[SEAL]

G. W. CUNNINGHAM,
Acting Commissioner of Narcotics.

[F.R. Doc. 56–1532; Filed, Feb. 28, 1956; 8:50 a.m.]

EXHIBIT D

DEPARTMENT OF THE TREASURY, BUREAU OF NARCOTICS

[21 CFR Part 305]

PROPOXYPHENE (4-DIMETHYLAMINO-1,2-DIPHENYL-3-METHYL-2-PROPIONOXYBUTANE)

FOUND NOT TO BE AN OPIATE

The Bureau of Narcotics published in the Federal Register (21 F.R. 1321) a notice of a proposed finding that the substance 4-dimethylamino-1.2-diphenyl-3-methyl-2-propionoxybutane (also known as propoxyphene) had an addiction-forming or addiction-sustaining liability similar to morphine and should be classified as an opiate. Eli Lilly and Company entered a protest with respect to the proposed findng and requested an opportunity to be heard on the matter. A hearing was held pursuant to this notice.

On the basis of all the evidence, including technical data offere at the hearing, plus the fact that there has been no evidence of any danger to the public welfare regarding addiction liability during the approximately five years propoxyphene has been on the market, I have concluded that this substance should not be found to be an opiate. Also taken into consideration in making this determination has been the resolution recommending such action, adopted at the January 1962 meeting of the Committee on Drug Addiction and Narcotics of the National Research Council, National Academy of Sciences.

[SEAL]

HENRY L. GIORDANO,
Acting Commissioner of Narcotics.

Approved: March 17, 1962.

JAMES A. REED,
Assistance Secretary of the Treasury.

[F.R. Doc. 62–2870; Filed, Mar. 23, 1962; 8:30 a.m.]

[21 CFR Part 307]

NORPETHIDINE (NORMEPERIDINE)

APPLICATIONS FOR LICENSE TO MANUFACTURE

Notice is hereby given pursuant to the provisions of section 8 of the Narcotics Manufacturing Act of 1960 (74 Stat. 62) and 21 CFR 307.93 that an application for a license to manufacture the narcotic drug Norpethidine (normeperidine), basic class No. 34, has been submitted by each of the following named companies:

Merck Chemical Division,
Merck & Co., Inc.,
126 East Lincoln Avenue,
Rahway, N.J.

Mallinckrodt Chemical Works,
Second and Mallinckrodt Streets,
St. Louis 7, Mo.

Winthrop Laboratories Division of Sterling Drug Co.,
1450 Broadway,
New York 18, N.Y.

and that such applications are being favorably considered.

Within twenty days from the date of publication of this notice in the Federal Register, any interested person may file a written protest with both the Commissioner of Narcotics and the applicants, against favorable consideration of the applications. Any such protest shall specify with particularity the facts relied upon as showing that the licenses if granted to the applicants would not be in the public interest. Such interested person at the time of filing may request a hearing as to his protest.

If no written notice of a desire to be heard shall be received within twenty days from date of publication of this notice in the Federal Register, no hearing shall be held.

[SEAL]

HENRY L. GIORDANO,
Acting Commissioner of Narcotics.

Approved: March 17, 1962.

JAMES A. REED,
Assistant Secretary of the Treasury.

[F.R. Doc. 62-2869; Filed Mar. 23, 1962; 8:50 a.m.]

EXHIBIT E

Wld Hlth Org. techn. Rep. Ser., 1964, 273

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 273

WHO EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Thirteenth Report

WORLD HEALTH ORGANIZATION
GENEVA

The World Health Organization (WHO) is a specialized agency of the United Nations. Its work is carried out by three organs : the World Health Assembly, the supreme authority, to which all Member States send delegates ; the Executive Board, the executive organ of the Health Assembly, consisting of 24 persons designated by as many Member States ; and a Secretariat under the Director-General.

WHO's activities include programmes relating to a wide variety of public health questions : communicable and chronic degenerative diseases, radiation and isotopes, maternal and child health, mental health, dental health, veterinary public health, social and occupational health, nutrition, nursing, environmental health, public health administration, professional education and training, and health education of the public. In addition, WHO undertakes or participates in certain technical work of international significance, such as the compilation of an international pharmacopoeia, the setting up of biological standards and of various other international standards (pesticides and pesticide-spraying equipment, drinking-water, food additives), the control of addiction-producing drugs, the exchange of scientific information and the publication of medical literature, the drawing up of international sanitary regulations, the revision of the international list of diseases and causes of death, the collection and dissemination of epidemiological information, and statistical studies on morbidity and mortality.

The Director-General has authority to establish expert advisory panels on particular subjects and to select and appoint their members, who undertake to contribute by correspondence and without remuneration information or reports on developments within their own specialties. They serve in their personal capacity and not as representatives of governments or other bodies. Expert committees are convened to advise on particular subjects ; their members are selected by the Director-General from the advisory panels, the choice being governed by the agenda of each committee. The selection of members of both expert advisory panels and committees is based primarily upon their ability and technical experience, with due regard to adequate geographical distribution.

Reports of expert committees, while not necessarily expressing the views of the Organization, are taken into consideration in developing programmes.

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES
No. 273

WHO EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Thirteenth Report

WORLD HEALTH ORGANIZATION
GENEVA
1964

WHO EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Geneva, 25-30 November 1963

Members : *

Dr N. B. Eddy, Consultant on Narcotics, National Institutes of Health, Bethesda, Md., USA (*Chairman*)

Dr L. Goldberg, Professor of Research on Alcohol and Analgesics, Karolinska Institutet, Stockholm, Sweden (*Rapporteur*)

Dr M. Granier-Doyeux, Professor of Pharmacology and Toxicology, Department of Pharmacology and Toxicology, Faculty of Medicine, Central University of Venezuela, Caracas, Venezuela

Dr P. Kielholz, Professor of Psychiatry, University of Basle, Switzerland

Dr A. D. Macdonald, Professor of Pharmacology, University of Manchester, England

Dr B. Mukerji, Director, Chittaranjan National Cancer Research Centre; Professor of Pharmacology, Calcutta, India

Dr V. V. Vasil'eva, Professor of Pharmacology, Second Moscow Institute of Medicine, Moscow, USSR (*Vice-Chairman*)

Representatives of the United Nations :

Mr W. J. Duke, Chief of Section, Division of Narcotic Drugs, United Nations, Geneva

Mr O. J. Braenden, Ph.D., Division of Narcotic Drugs, United Nations, Geneva

Representative of the Permanent Central Opium Board and the Drug Supervisory Body :

Mr A. Lande, Dr jur., Secretary of these two bodies, Geneva

Secretariat :

Dr H. Halbach, Dr med., Dr Ing., Chief Medical Officer, Addiction-Producing Drugs, WHO (*Secretary*)

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* Unable to attend :

Dr G. Joachimoglu, Professor Emeritus of Pharmacology; formerly Chairman, Superior Health Council, Ministry of Social Welfare, Athens, Greece

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Wld Hlth Org. techn. Rep. Ser., 1964, 273

WHO EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Thirteenth Report

The WHO Expert Committee on Addiction-Producing Drugs met in Geneva from 25-30 November 1963.

Dr P. Dorolle, Deputy Director-General, on behalf of the Director-General, opened the session and welcomed the members of the Committee, the representatives of the Secretary-General of the United Nations, and the representative of the Permanent Central Opium Board and the Drug Supervisory Body. Dr N. B. Eddy was elected Chairman, Dr V. V. Vasil'eva Vice-Chairman, and Dr L. Goldberg Rapporteur.

1. Notifications

1.1 *1-Dimethylamino-3-phenylindane* [1]

Referring to the notification of the Government of Canada, the Committee considered the accompanying reports, which included data on tests for physical dependence carried out with 1-dimethylamino-3-phenylindane in the monkey and in man. In view of the negative character of the evidence submitted and in the absence of any indication of the convertibility of 1-dimethylamino-3-phenylindane into a product capable of producing addiction, the Committee was of the opinion that 1-dimethylamino-3-phenylindane should not now be regarded either as an addiction-producing drug or as one capable of conversion into an addiction-producing drug. Therefore,

The WHO Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to 1-dimethylamino-3-phenylindane be communicated to the Secretary-General of the United Nations.

1.2 *Droxypropine* [2]

In its twelfth report,[3] the Committee considered that the information at its disposal was insufficient for it to reach a definite conclusion with respect

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[1] Also designated as *N,N*-dimethyl-3-phenyl-1-indanamine.

[2] International non-proprietary name proposed for 1-[2-(2-hydroxyethoxy)ethyl]-4-phenyl-4-propionylpiperidine.

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1962, 229, 4 (section 1.2).

to the addiction liability of droxypropine and decided to defer its opinion. Data on tests for physical dependence in the monkey have now been supplemented by clinical tests. In the light of the negative character of the evidence presented and in the absence of any indication of the convertibility of droxypropine into a product capable of producing addiction, the Committee concluded that droxypropine should not now be regarded as an addiction-producing drug or as one capable of conversion into an addiction-producing drug. Therefore,

The WHO Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to droxypropine be communicated to the Secretary General of the United Nations.

1.3 *Fentanyl* [1]

Referring to the notification of the Government of Belgium, the Committee considered that fentanyl (1) produced morphine-like effects, and (2) can be substituted for morphine in a known addiction. Evidence on these points was derived in part from experiments in monkeys. Experience has shown that results obtained in the monkey correlate with those in man, so that, when the former are unequivocal, they may be accepted as evidence of what is to be expected in man. Consequently, the Committee was of the opinion that fentanyl must be considered to be an addiction-producing drug comparable to morphine and that fentanyl and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The WHO Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to fentanyl and its salts be communicated to the Secretary General of the United Nations.

1.4 *Norpipanone* [2]

Referring to the notification of the Government of Hungary, the Committee considered that norpipanone (1) produced morphine-like effects, and (2) can be substituted for morphine in a known addiction. Evidence on these points was derived in part from experiments in monkeys. Experience has shown that results obtained in the monkey correlate with those in man, so that, when the former are unequivocal, they may be accepted as evidence of what is to be expected in man. In addition, the chemical

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[1] International non-proprietary name proposed for 1-phenethyl-4-*N*-propionylanilinopiperidine.

[2] International non-proprietary name proposed for 4,4-diphenyl-6-piperidino-3-hexanone.

structure of norpipanone bears an extremely close relationship to that of other drugs known to be addiction producing.[1] Consequently the Committee was of the opinion that norpipanone must be considered to be an addiction-producing drug comparable to morphine and that norpipanone and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The WHO Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to norpipanone and its salts be communicated to the Secretary-General of the United Nations.

1.5 *Dextropropoxyphene* [2]

The Committee considered again the evidence with respect to the abuse liability of dextropropoxyphene.[3] It concluded that on the basis of five years of marketing experience and repeated observations at the Addiction Research Center, Lexington, Ky., USA, in comparison with other substances, the risk of dextropropoxyphene to public health appeared to be sufficiently low as not now to require international narcotics control.

2. Work of International Bodies concerned with Narcotic Drugs

2.1 The reports of the seventeenth [4] and eighteenth [5] sessions of the Commission on Narcotic Drugs of the Economic and Social Council, the relevant resolutions of the Economic and Social Council,[6] and the reports of the Permanent Central Opium Board [7, 8] and Drug Supervisory Body [9] were

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1956, 102, 10 (section 5.2.3).

[2] International non-proprietary name for (+)-4-dimethylamino-3-methyl-1,2-diphenyl-2-propionoxybutane.

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1958, 142, 7 (section 5.1.3).

[4] United Nations, Commission on Narcotic Drugs (1962) *Report of the Seventeenth Session (May-June 1962)—(Economic and Social Council. Official Records : thirty-fourth session. Supplement No. 9)*, Geneva (Document E/3648).

[5] United Nations, Commission on Narcotic Drugs (1963) *Report of the Eighteenth Session (April-May 1963)—(Economic and Social Council. Official Records : thirty-sixth session. Supplement No. 9)*, Geneva (Document E/3775).

[6] United Nations, Economic and Social Council (1963) *Official Records : thirty-sixth session, 2 July - 2 August 1963. Supplement No. 1 : Resolutions*, Geneva, p. 21 (Document E/3816).

[7] United Nations, Permanent Central Opium Board (1961) *Report to the Economic and Social Council on the Work of the Board in 1961*, Geneva (Document E/OB/17).

[8] United Nations, Permanent Central Opium Board (1962) *Report to the Economic and Social Council on the Work of the Board in 1962*, Geneva (Document E/OB/18).

[9] United Nations, Drug Supervisory Body (1961, 1962) *Estimated World Requirements for Narcotic Drugs in 1962 and 1963*, Geneva (Documents E/DSB/19 & 20).

summarized by the Secretary. Several items referred to in these reports were relevant to the Committee's present agenda.

2.2 With reference to the recent regional conference on coca leaf problems and the relevant resolution of the Economic and Social Council,[1] the Committee noted with satisfaction that there is now general agreement on the harmfulness of coca leaf chewing and that the problems connected therewith are to be regarded as a concomitant of unfavourable socio-economic circumstances, with detrimental effects on the individual as well as the society. The general acceptance of this point of view should help in directing efforts towards the betterment of the underlying environmental conditions, wherever possible as part of the general social and economic development of the areas concerned, and towards the eventual solution of the coca leaf problem.

2.3 With reference to the economic significance of coca leaves arising out of a possible increase in the legal production of cocaine for medical purposes, the Committee wished to draw attention to the fact that the medical needs for cocaine have decreased considerably in the past few decades, as a consequence of the continuing development of synthetic local anaesthetics which can replace cocaine in the majority of its therapeutic indications. Therefore, further reduction in the legal manufacture of cocaine is likely and desirable, and this should diminish opportunity for diversion to illicit uses. The Committee was disturbed by the fact that in spite of this there is an upward trend in the abuse of cocaine, particularly in combination with other drugs.

2.4 The Committee was glad to note that the Commission on Narcotic Drugs and the Permanent Central Opium Board [2] were now placing increased emphasis on the sociological and economic aspects of drug abuse. It expressed the hope that the Commission's resolution [3] requesting member states of the United Nations or of the specialized agencies to encourage research on these aspects of the problem would contribute to the elucidation of the epidemiology of drug abuse already called for both by the WHO Expert Committee on Addiction-Producing Drugs [4] and by the WHO Study Group on the Treatment and Care of Drug Addicts.[5]

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[1] United Nations, Economic and Social Council (1963) *Official Records: thirty-sixth session, 2 July - 2 August 1963. Supplement No. 1: Resolutions*, Geneva, p. 21 (Document E/3816).

[2] United Nations, Permanent Central Opium Board (1963) *Report to the Economic and Social Council on the Work of the Board in 1963*, Geneva (Document E/OB/19).

[3] United Nations Commission on Narcotic Drugs (1962) *Report of the Seventeenth Session, Resolution 2 (XVII)* (Document E/3648, p. 22).

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1960, 188, 11.

[5] *Wld Hlth Org. techn. Rep. Ser.*, 1957, 131, 11.

2.5 In connexion with the Commission's resolution on the control of barbiturates [1] the Committee wished to point out that there were a number of non-barbiturate sedatives, hypnotics and other drugs with sedative effect which had been shown to be abused and to produce ill-effects similar to those of the barbiturates. This was of particular significance where the sedative effect was not the one for which the drug was primarily used in medicine, but could be made use of properly under some circumstances, and might also lead to abuse. This may be illustrated by certain of the antihistamines developed as anti-allergic agents, but exhibiting sufficient sedative action to be used, and abused, as sedatives. Another pertinent case is the recent observation of an epidemic-like outbreak of abuse of hypnotic drugs in a particular region. Methaqualone originally developed as an antimalarial is currently advertised as a sedative and although introduced into that region only a year ago is now reported to constitute about four-fifths of the total amount of hypnotic drugs abused in the group studied.

2.6 Sudden changes in the drug of choice for abuse amongst groups within a population or in circumscribed areas such as referred to above tend to show, in the Committee's view, the relevance of sociological and environmental factors, as distinct from individual motives, in the etiology of drug abuse. Such fluctuations thus indicate the need for immediate national control measures, as repeatedly recommended by the Committee, for drugs of abuse not under international control (barbiturates [2] or other sedatives [3] and amphetamines [4]).

2.7 With regard to the proposal made in the Commission on Narcotic Drugs for an investigation into the causative role of psychoactive substances in accidents, especially road accidents, the Committee believed that such investigations could profitably be combined with similar studies on the role of alcohol.

2.8 The Committee took cognizance of the 1963 edition of the *Multilingual list of narcotic drugs under international control*.[5] The list has been greatly expanded, partly by the inclusion of names of new drugs, but more particularly by additional names for drugs already known. The list is a helpful tool for anybody working in this field. The Committee hopes that this document will be kept up to date.

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[1] United Nations Commission on Narcotic Drugs (1962) *Report of the Seventeenth Session, Resolution 4 (XVII)* (Document E/3648, p. 31).

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1957, 116, 10 (sections 9 & 10).

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1958, 142, 10 (section 6).

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1961, 211, 9 (section 2.2).

[5] United Nations (1963) *Narcotic drugs under international control. Multilingual list* (Document E/CN.7/436).

3. Single Convention on Narcotic Drugs, 1961

3.1 In the course of the preparations for the coming into force of the Single Convention, WHO was invited [1] to make recommendations regarding amendments to the schedules annexed to that treaty instrument. The Committee considered the following changes necessary.

3.2 *Schedule I*

The following items should be added:

Fentanyl (1-phenethyl-4-N-propionylanilinopiperidine)
Methadone-Intermediate (4-cyano-2-dimethylamino-4,4-diphenylbutane)
Moramide-Intermediate (2-methyl-3-morpholino-1,1-diphenylpropane carboxylic acid)
Noracymethadol ((±)-α-3-acetoxy-6-methylamino-4,4-diphenylheptane)
Norpipanone (4,4-diphenyl-6-piperidine-3-hexanone)
Pethidine-Intermediate-A (4-cyano-1-methyl-4-phenylpiperidine)
Pethidine-Intermediate-B (4-phenylpiperidine-4-carboxylic acid ethyl ester)
Pethidine-Intermediate-C (1-methyl-4-phenylpiperidine-4-carboxylic acid)

The following text should be added (after the entry " Trimeperidine "):

" Any other product obtained from any of the phenanthrene alkaloids of opium or ecgonine alkaloids of the coca leaf, not listed in Schedule I or II, and neither made nor utilized exclusively for authorized domestic research, unless the government concerned finds that the product in question does not have morphine-like or cocaine-like effects. "

In the entry " Concentrate of Poppy Straw " the words " when such material is made available in trade " should be deleted.

3.3 *Schedule II*

Nicocodine (6-nicotinylcodeine) should be added.

Dextropropoxyphene ((+)-4-dimethylamino-3-methyl-1,2-diphenyl-2-propionoxybutane) should be deleted.

3.4 *Schedule III*

Of the substances listed in section (1), dextropropoxyphene should be deleted.

The rest of section (1) should read as follows:

" When compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in individual preparations. "

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[1] United Nations, Commission on Narcotic Drugs (1962) *Report of the Seventeenth Session (May-June 1962)—Economic and Social Council, Official Records, thirty-fourth session, Supplement No. 9*, Geneva (Document E/3648, p. 36).

In section (2) the following words should be deleted :

" in such a way that the preparation has no, or a negligible, risk of abuse, and in such a way that the drug cannot be recovered by readily applicable means in a yield which would constitute a risk to public health. "

In section (3) the words " Solid dose " should be deleted.

4. Terminology in Regard to Drug Abuse

" Drug dependence " to replace the terms " drug addiction " and " drug habituation "

The WHO Expert Committee on Addiction-Producing Drugs in 1952 [1] attempted to formulate a definition of addiction applicable to drugs under international control, which it later (1957) [2] revised. The Expert Committee sought also to differentiate addiction from habituation and wrote a definition of the latter which, however, failed in practice to make a clear distinction. The definition of addiction gained some acceptance, but confusion in the use of the terms addiction and habituation and misuse of the former continued. Further, the list of drugs abused increased in number and diversity. These difficulties have become increasingly apparent and various attempts have been made to find a term that could be applied to drug abuse generally. The component in common appears to be dependence, whether psychic or physical or both. Hence, use of the term " drug dependence ", with a modifying phrase linking it to a particular drug type in order to differentiate one class of drugs from another, has been given most careful consideration.

" Drug dependence " is defined as a state arising from repeated administration of a drug on a periodic or continuous basis. Its characteristics will vary with the agent involved and this must be made clear by designating the particular type of drug dependence in each specific case—for example, drug dependence of morphine type, of cocaine type, of cannabis type, of barbiturate type, of amphetamine type, etc. (See Annex 1 for descriptions of specific types of drug dependence.)

The Expert Committee recommends substitution of the term " drug dependence " for the terms " drug addiction " and " drug habituation ".

It must be emphasized that drug dependence is a general term selected for its applicability to all types of drug abuse and carries no connotation of the degree of risk to public health or need for a particular type of drug control. The agents controlled internationally continue to be those that are morphine-like, cocaine-like, and cannabis-like, however produced, the use of which results in drug dependence of morphine type, drug dependence

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1952, 57, 9 (section 6.1).

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1957, 116, 9 (section 8).

of cocaine type, and drug dependence of cannabis type. Other types of drug dependence (barbiturate, amphetamine, etc.) continue to present problems, but their description under the general term "drug dependence" does not in any way affect the measures taken to solve them. The general term will help to indicate a relationship by drawing attention to a common feature associated with drug abuse and at the same time permit more exact description and differentiation of specific characteristics according to the nature of the agent involved.

5. Considerations Governing the Medical Use of Narcotics

The Committee has on many occasions stressed the medical aspects of the treatment of addicts and the precautionary attitude that should be adopted by physicians in this connexion and in the use of narcotics generally in their practice. Its attention was drawn to a recent report setting forth in considerable detail the whole philosophy of the use of narcotics in medical practice.[1] It was felt that this report constituted a useful guide towards the attainment of the objectives that the Committee has stressed.

6. Khat (*Catha edulis*)

The Committee studied a report by the Secretariat on the medical aspects of the habitual chewing of khat leaves. In this report the somatic and psychic symptoms brought about by the chewing of the leaves were reviewed and explained as the effects of the specific active principles contained in the leaves. Besides tannins in appreciable amounts, it has been possible to identify (+)-norpseudoephedrine (cathine) and a chemically and pharmacologically closely related substance, which disappears when the plant is dried and is presumably a step in the biosynthesis of cathine. These two substances are amphetamine-like in respect of structure and pharmacodynamics, but there is evidence that their effects are less powerful than those produced by equivalent amounts of, for example, methamphetamine.

The Committee considered that while khat and pure amphetamine substances produced medical effects that were similar although of different degree, the lower activity of khat was due in the main to differences in dosage, route of administration, and the circumstances in which the one or the other were consumed. In addition, khat produced gastro-intestinal symptoms, due partly to its high content of tannins.

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[1] Council on Mental Health (1963) *Narcotics and medical practice. J. Amer. med. Ass.*, 185, 976.

The Committee realized that the habitual chewing of khat had led, in some areas, to socio-economic phenomena detrimental to the individual and the community, such as loss of man hours and diversion of income, with malnutrition and aggravation of disease as consequences.

The Committee was of the opinion that the problems connected with khat and with the amphetamines [1] should be considered in the same light because of the similarity of their medical effects, even though there are quantitative differences and specific socio-economic features; this is all the more desirable since the problems with respect to khat are confined at present to a few countries in one region.

7. Abuse of Hallucinogenic Agents

The Committee took note of the increasingly frequent reports of poorly controlled clinical administration and non-medical use of lysergic acid diethylamide (LSD-25). In spite of warnings, irregular use is reaching alarming proportions. The Committee was particularly disturbed by the publicity given to the uncontrolled use of this drug and the damage that the indiscriminate use of so powerful an agent has already produced. The problem is at present a local one. In the Committee's opinion, immediate measures with respect to distribution and availability are necessary.

Other instances of indiscriminate use of agents with related effects, such as peyotl (mescaline), *Piptadenia peregrina* (bufotenine), and *Rivea corymbosa* were noted. The misuse in these instances appears to be less widespread than in the case of LSD-25, but a watch should be kept and corrective measures taken where necessary.

8. Coded Information on Narcotics

As indicated in previous reports,[2-5] the Committee maintains an interest in the availability of a centralized source of information on drug dependence in all its aspects, including the agents involved, with easy means of fast retrieval.

Coded data (about 8000 items) on a large part of the material accumulated, have now been transferred to an IBM card system, and the complete bibliographic material microfilmed. Co-operation with the American

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1956, 102, 12 (section 7); 1957, 116, 9 (section 7).
[2] *Wld Hlth Org. techn. Rep. Ser.*, 1957, 116, 11 (section 11).
[3] *Wld Hlth Org. techn. Rep. Ser.*, 1958, 142, 11 (section 9).
[4] *Wld Hlth Org. techn. Rep. Ser.*, 1959, 160, 10 (section 7), 14 (Annex 2).
[5] *Wld Hlth Org. techn. Rep. Ser.*, 1962, 229, 12 (section 8).

Social Health Association, the Alcoholism and Drug Addiction Research Foundation, Toronto, and the United Nations Division of Narcotic Drugs, has been worked out. This will greatly expedite further work and increase the completeness of coverage of published material in this field. Sets of IBM cards and the microfilm will shortly be available at cost.

9. International Classification of Diseases

The Committee was informed of the preparation of the eighth revision of the classification, and would draw attention to the diversity of the items listed under "316. Drug Addiction", not all of which are considered addiction-producing in a legal or pharmacological sense. Referring to the recommendation in the present report that the term "drug dependence" be substituted for "drug addiction", the Committee would invite attention to the application of this recommendation in the international classification of diseases, thereby bringing into better harmony the list of diverse items referred to above.

Annex 1

TYPES OF DRUG DEPENDENCE

Drug dependence of morphine type is described as a state arising from repeated administration of morphine, or an agent with morphine-like effects, on a periodic or continuous basis. Its characteristics include:

(1) an overpowering desire or need to continue taking the drug and to obtain it by any means; the need can be satisfied by the drug taken initially or by another with morphine-like properties;

(2) a tendency to increase the dose owing to the development of tolerance;

(3) a psychic dependence on the effects of the drug related to a subjective and individual appreciation of those effects; and

(4) a physical dependence on the effects of the drug requiring its presence for maintenance of homeostasis and resulting in a definite, characteristic, and self-limited abstinence syndrome when the drug is withdrawn.

The abstinence syndrome is the most characteristic and distinguishing feature of drug dependence of morphine type. It appears within a few hours of the last dose of drug taken, reaches peak intensity in 12 hours or more, and subsides spontaneously, most often within a week, the time course varying with the duration of action of the specific morphine-like agent involved. The abstinence syndrome may also be precipitated in a matter of minutes and made to take a more rapid time course by the administration of a specific antagonist while continuing the administration of the agent responsible for the dependence. The complex of symptoms which constitute the abstinence syndrome includes: yawning, lacrimation, rhinorrhoea, perspiration, mydriasis, tremor, gooseflesh, anorexia, anxiety, restlessness, nausea, emesis, diarrhoea, hot flushes, rise in body temperature, increase in respiratory rate and in systolic blood pressure, abdominal or other muscle cramps, and dehydration and loss of body-weight.

Drug dependence of barbiturate type is described as a state arising from repeated administration of a barbiturate, or an agent with barbiturate-like effect, on a continuous basis, generally in amounts exceeding therapeutic dose levels. Its characteristics include:

(1) a strong desire or need to continue taking the drug; the need can be satisfied by the drug taken initially or by another with barbiturate-like properties;

(2) a tendency to increase the dose, partly owing to the development of tolerance;

(3) a psychic dependence on the effects of the drug related to subjective and individual appreciation of those effects; and

(4) a physical dependence on the effects of the drug requiring its presence for maintenance of homeostasis and resulting in a definite, characteristic, and self-limited abstinence syndrome when the drug is withdrawn.

The abstinence syndrome is the most characteristic and distinguishing feature of drug dependence of barbiturate type. It begins to appear within the first 24 hours of cessation of drug taking, reaches peak intensity in two or three days, and subsides slowly. There is at present no known agent that will precipitate the barbiturate abstinence syndrome during continuation of drug administration. The complex of symptoms which constitute the abstinence syndrome, in approximate order of appearance, are: anxiety, involuntary twitching of muscles, intention tremor of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia, weight loss, and a precipitous drop in blood pressure on standing; convulsions of a grand mal type and/or a delirium resembling alcoholic delirium tremens may occur.

Drug dependence of cocaine type is described as a state arising from repeated administration of cocaine or an agent with cocaine-like properties, on a periodic or continuous basis. Its characteristics include:

(1) an overpowering desire or need to continue taking the drug and to obtain it by any means;

(2) absence of tolerance to the effects of the drug during continued administration; in the more frequent episodic use, the drug may be taken at short intervals, resulting in the build-up of an intense toxic reaction;

(3) a psychic dependence on the effects of the drug related to a subjective and individual appreciation of those effects; and

(4) absence of a physical dependence and hence absence of an abstinence syndrome on abrupt withdrawal; withdrawal is attended by a psychic disturbance manifested by craving for the drug.

Drug dependence of amphetamine type is a state arising from repeated administration of amphetamine or an agent with amphetamine-like effects on a periodic or continuous basis. Its characteristics include:

(1) a desire or need to continue taking the drug;

(2) consumption of increasing amounts to obtain greater excitatory and euphoric effects or to combat more effectively depression and fatigue, accompanied in some measure by the development of tolerance;

(3) a psychic dependence on the effects of the drug related to a subjective and individual appreciation of the drug's effects; and

(4) general absence of physical dependence so that there is no characteristic abstinence syndrome when the drug is discontinued.

Drug dependence of cannabis type is described as a state arising from repeated administration of cannabis or cannabis substances, which in some areas is almost exclusively periodic, in others more continuous. Its characteristics include:

(1) a desire (or need) for repeated administration of the drug on account of its subjective effects, including the feeling of enhanced capabilities;

(2) little or no tendency to increase the dose, since there is little or no development of tolerance;

(3) a psychic dependence on the effects of the drug related to subjective and individual appreciation of those effects;

(4) absence of physical dependence so that there is no definite and characteristic abstinence syndrome when the drug is discontinued.

These are concise descriptions which could be expanded, particularly with reference to differences in degree according to dose and duration of administration and to potency among agents within a particular type. The differences between morphine and codeine are a good example of the latter. Descriptions of drug dependence of other types could be written, e.g., for certain sedatives not chemically classified as barbiturates, or for alcohol, to name only two. The characteristics of dependence of the non-barbiturate sedative type are essentially identical with the characteristics of dependence of the barbiturate type and a separate description seems at present unnecessary. Alcohol is outside the terms of reference of this expert committee, but is nevertheless an agent that can admittedly cause psychic and physical dependence.

All the descriptions of types of drug dependence have been confined to medical aspects only, but socio-economic characteristics and implications should not be overlooked. They vary according to the drug type and there are variations in the individual and social harm that accompany drug dependence of different types:

With morphine, the harm to the individual is in the main indirect, arising from preoccupation with drug taking; personal neglect, malnutrition and infection are frequent consequences. For society also, the harm may be related to the preoccupation of the individual with drug taking; disruption of interpersonal relationships, economic loss, and crimes against property are frequent consequences.

With the barbiturates, the detrimental effect on the individual stems in part from his preoccupation with drug taking, but more particularly from

persistent effects of the drug—ataxia, dysarthria, and impairment of mental function, with confusion, loss of emotional control, poor judgment, and occasionally a toxic psychosis. The harm to society is related to both the individual's preoccupation with drug taking and the drug's effect on interpersonal relationships.

With cocaine, the individual detrimental effect may be indirect, resulting from the individual's preoccupation with drug taking, again with malnutrition and infection as frequent consequences, or direct, a severe toxic reaction accompanying rapid and repeated administration in episodic drug use. The harm to society is related to preoccupation with drug taking by the individual, with economic loss and crimes against society as consequences. When drug dependence of cocaine type is brought about through chewing of coca leaves, anorexia, a change in working habits, and loss in weight are additional characteristics.

The amphetamines tend to cause anorexia, persistent and exaggerated psychomotor disturbances, and disruption of mental function, even to the occurrence of a toxic psychosis. For society, the harm is related in part to the drug's psychomotor effects (involvement in accidents, for example).

With cannabis, lasting disturbance of mental function has been alleged but not proven. Distortion of perception, one of the effects of the drug, may lead to disruption of interpersonal relationships, and abuse of the drug to criminal behaviour.

The risk to public health should be and usually is of paramount importance as a criterion for the establishment of control for a dependence-producing drug of any of the types described and in deciding on the degree of control. At the same time, socio-economic factors and social harm associated with drug dependence and drug abuse must be taken into account and may determine the appropriateness of control in a particular case. The socio-economic factors largely determine society's attitude towards the individuals involved in drug abuse, but they are not characteristics that need to be considered in medical and scientific differentiation of the types of drug dependence.

Annex 2

LIST OF DRUGS UNDER INTERNATIONAL NARCOTICS CONTROL[1]

Common name or INN *	*Chemical designation*	*Expert Committee on Addiction-Producing Drugs*		*Control regime*	
		Report number	*Reference* [2]	*Group*	*Co ventı*
acetyldihydrocodeine	acetyldihydrocodeine	1	1949, 19, 30	II	193
acetylmethadol *	3-acetoxy-6-dimethylamino-4,4-diphenylheptane	1	1949, 19, 31	I	193
allylprodine *	3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine	10	1960, 188, 3	I	193
alphacetylmethadol *	α-3-acetoxy-6-dimethylamino-4,4-diphenylheptane	4	1954, 76, 7	I	193
alphameprodine *	α-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine	7	1957, 116, 8	I	193
alphamethadol *	α-6-dimethylamino-4,4-diphenyl-3-heptanol	4	1954, 76, 7	I	193
alphaprodine *	α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine	1	1949, 19, 30	I	193
anileridine *	1-(*p*-aminophenethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	7	1957, 116, 7	I	193
benzethidine *	1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	10	1960, 188, 4	I	193
benzylmorphine	3-benzylmorphine			I	193
betacetylmethadol *	β-3-acetoxy-6-dimethylamino-4,4-diphenylheptane	4	1954, 76, 7	I	193
betameprodine *	β-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine	3	1952, 57, 7	I	193
betamethadol *	β-6-dimethylamino-4,4-diphenyl-3-heptanol	5	1955, 95, 8	I	193
betaprodine *	β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine	1	1949, 19, 30	I	193
cannabis	*Cannabis sativa* L.				192
clonitazene *	2-*p*-chlorbenzyl-1-diethylaminoethyl-5-nitrobenzimidazole	11	1961, 211, 4	I	193
cocaine	methyl ester of benzoylecgonine			I	193
coca leaf					192
codeine	3-methylmorphine			II	193
codeine-N-oxide				I	193
desomorphine *	dihydrodeoxymorphine			I	193
dextromoramide *	(+)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine	8	1958, 142, 8	I	193

* Proposed international non-proprietary name (INN).

[1] For details such as synonyms and the date of coming into force of international control, *Multilingual list of narcotic drugs under international control* (UN document E/CN 7/341) and *L of drugs under international control* (published annually by the UN, Division of Narcotic Dru respectively.

[2] The references given in this column are to *World Health Organization : Technical Report Ser* with the exception of the report published in 1949 which appeared in *Official Records of the Wo Health Organization*, No. 19.

Common name or INN •	*Chemical designation*	*Expert Committee on Addiction-Producing Drugs*		*Control regime*	
		Report number	*Reference* [1]	*Group*	*Convention*
diampromide •	*N*-[2-(methylphenethylamino)-propyl]-propionanilide	11	1961, 211, 5	I	1931
diethylthiambutene •	3-diethylamino-1,1-di-(2'-thienyl)-1-butene	6	1956, 102, 10	I	1931
dihydrocodeine	7,8-dihydrocodeine	1	1949, 19, 30	II	1931
dihydromorphine	7,8-dihydromorphine			I	1931
dihydromorphine esters				I	1931
dimenoxadol •	2-dimethylaminoethyl 1-ethoxy-1,1-diphenylacetate	9	1959, 160, 9	I	1931
dimepheptanol •	6-dimethylamino-4,4-diphenyl-3-heptanol	1	1949, 19, 31	I	1931
dimethylthiambutene •	3-dimethylamino-1,1-di-(2'-thienyl)-1-butene	4	1954, 76, 9	I	1931
dioxaphetyl butyrate •	ethyl 4-morpholino-2,2-diphenylbutyrate	6	1956, 102, 9	I	1931
diphenoxylate •	1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	11	1961, 211, 5	I	1931
dipipanone •	4,4-diphenyl-6-piperidino-3-heptanone	5	1955, 95, 8	I	1931
ecgonine	(—)-3-hydroxytropane-2-carboxylate			I	1931
ecgonine esters				I	1931
ethylmethylthiambutene •	3-ethylmethylamino-1,1-di-(2'-thienyl)-1-butene	4	1954, 76, 9	I	1931
ethylmorphine	3-ethylmorphine			II	1931
etonitazene •	1-diethylaminoethyl-2-*p*-ethoxybenzyl-5-nitrobenzimidazole	11	1961, 211, 7	I	1931
etoxeridine •	1-[2-(2-hydroxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester	8	1958, 142, 9	I	1931
fentanyl •	1-phenethyl-4-*N*-propionylanilinopiperidine	13	1964, 273, 4	I	1931
furethidine •	1-(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	10	1960, 188, 5	I	1931
heroin	diacetylmorphine			I	1931
hydrocodone •	dihydrocodeinone			I	1931
hydrocodone esters				I	1931
hydromorphinol •	14-hydroxydihydromorphine	11	1961, 211, 7	I	1931
hydromorphone •	dihydromorphinone				1925
hydromorphone esters					1925
hydroxypethidine •	4-(*m*-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid ethyl ester	1	1949, 19, 30	I	1931
isomethadone •	6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone	1	1949, 19, 31	I	1931
ketobemidone •	4-(*m*-hydroxyphenyl)-1-methyl-4-propionylpiperidine	1	1949, 19, 30	I	1931
levomethorphan •	(—)-3-methoxy-*N*-methylmorphinan	3	1952, 57, 6	I	1931

[1] The references given in this column are to *World Health Organization : Technical Report Series*, with the exception of the report published in 1949 which appeared in *Official Records of the World Health Organization*, No. 19.

Common name or INN *	Chemical designation	Expert Committee on Addiction-Producing Drugs		Control regime	
		Report number	Reference [1]	Group	Convention
levomoramide *	(−)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)-butyl]morpholine	8	1958, 142, 8	I	1931
levophenacylmorphan *	(−)-3-hydroxy-*N*-phenacylmorphinan	10	1960, 188, 5	I	1931
levorphanol *	(−)-3-hydroxy-*N*-methylmorphinan	3	1952, 57, 6	I	1931
metazocine *	2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan	10	1960, 188, 6	I	1931
methadone *	6-dimethylamino-4,4-diphenyl-3-heptanone	1	1949, 19, 30	I	1931
methadone-intermediate	4-cyano-2-dimethylamino-4,4-diphenylbutane	12	1962, 229, 7	I I	1931 1931
methyldesorphine *	6-methyl-Δ^6-deoxymorphine	4	1954, 76, 6	I	1931
methyldihydromorphine *	6-methyldihydromorphine	5	1955, 95, 5	I	1931
metopon *	5-methyldihydromorphinone	1	1949, 19, 30	I	1931
moramide-intermediate	2-methyl-3-morpholino-1,1-diphenylpropane carboxylic acid	12	1962, 229, 7	I	1931
morpheridine *	1-(2-morpholinoethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	8	1958, 142, 8	I	1931
morphine				I	1931
morphine esters				I	1931
morphine ethers				I	1931
morphine-N-oxide				I	1931
morphine-N-oxide derivatives				I	1931
morphine pentavalent nitrogen derivatives				I	1931
myrophine *	myristylbenzylmorphine	5	1955, 95, 6	II	1931
nicocodine *	6-nicotinylcodeine	12	1962, 229, 6	II	1931
nicomorphine *	3,6-dinicotinylmorphine	9	1959, 160, 4	I	1931
noracymethadol *	(±)-α-3-acetoxy-6-methylamino-4,4-diphenylheptane	12	1962, 229, 5	I	1931
norcodeine *	*N*-demethylcodeine	9	1959, 160, 5	II [2]	1931
norlevorphanol *	(−)-3-hydroxymorphinan	10	1960, 188, 6	I	1931
normethadone *	6-dimethylamino-4,4-diphenyl-3-hexanone	5	1955, 95, 7	I	1931
normorphine *	demethylmorphine	9	1959, 160, 5	I	1931
norpipanone *	4,4-diphenyl-6-piperidino-3-hexanone	13	1964, 273, 4	I	1931
opium					1925
oxycodone *	14-hydroxydihydrocodeinone			I	1931
oxycodone esters				I	1931
oxymorphone *	14-hydroxydihydromorphinone	5	1955, 95, 6	I	1931
pethidine *	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester	1	1949, 19, 30	I	1931

[1] The references given in this column are to *World Health Organization : Technical Report Series* with the exception of the report published in 1949 which appeared in *Official Records of the World Health Organization*, No. 19.

[2] Recommended by WHO for this control regime.

Common name or INN *	Chemical designation	Expert Committee on Addiction-Producing Drugs		Control regime	
		Report number	Reference [1]	Group	Convention
pethidine-intermediate-A	4-cyano-1-methyl-4-phenylpiperidine	12	1962, 229, 7	I	1931
pethidine-intermediate-B	4-phenylpiperidine-4-carboxylic acid ethyl ester	12	1962, 229, 7	I	1931
pethidine-intermediate-C	1-methyl-4-phenylpiperidine-4-carboxylic acid			I	1931
pethidine-intermediate-C, esters of		5	1955, 95, 9	I	1931
phenadoxone *	6-morpholino-4,4-diphenyl-3-heptanone	1	1949, 19, 31	I	1931
phenampromide *	*N*-(1-methyl-2-piperidinoethyl)propionanilide	11	1961, 211, 7	I	1931
phenazocine *	2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan	10	1960, 188, 6	I	1931
phenomorphan *	3-hydroxy-*N*-phenethylmorphinan	6	1956, 102, 8	I	1931
phenoperidine *	1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	11	1961, 211, 8	I	1931
pholcodine *	morpholinylethylmorphine	3	1952, 57, 5	II	1931
piminodine *	4-phenyl-1-(3-phenylaminopropyl)piperidine-4-carboxylic acid ethyl ester	10	1960, 188, 7	I	1931
proheptazine *	1,3-dimethyl-4-phenyl-4-propionoxyazacycloheptane	6	1956, 102, 11	I	1931
properidine *	1-methyl-4-phenylpiperidine-4-carboxylic acid isopropyl ester	5	1955, 95, 9	I	1931
racemethorphan *	(±)-3-methoxy-*N*-methylmorphinan	3	1952, 57, 7	I	1931
racemoramide *	(±)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)-butyl]morpholine	8	1958, 142, 8	I	1931
racemorphan *	(±)-3-hydroxy-*N*-methylmorphinan	3	1952, 57, 6	I	1931
thebacon *	acetyldihydrocodeinone			I	1931
thebaine	3,6-dimethyl-8-dehydromorphine			I	1931
trimeperidine *	1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine	8	1958, 142, 9	I	1931

[1] The references given in this column are to *World Health Organization : Technical Report Series*, with the exception of the report published in 1949 which appeared in *Official Records of the World Health Organization*, No. 19.

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[From the Federal Register, vol. 44, No. 43, Mar. 2, 1979]

[Docket No. 77N-0266; DESI 10996]

PROPOXYPHENE

PUBLIC HEARING

Agency: Food and Drug Administration (FDA).

Action: Notice of Public Hearing.

Summary: The Commissioner of Food and Drugs announces that FDA will hold a public hearing to receive information and opinions from interested persons on the issues of the safety and effectiveness of propoxyphene-containing drug product and whether additional regulatory action is needed in regard to these drugs. The hearing is part of an extensive review of propoxyhene undertaken at the direction of the Secretary.

Dates: The public hearing will be held on April 6, 1979, at 9 a.m. Written or oral notices of participation are due no later than March 23, 1979.

Address: The public hearing will be held at the Snow Room (Room 5051), HEW North Building, 330 Independence Avenue SW, Washington, D.C.

Written notices of participation should be sent to the Hearing Clerk (HFA-305), Food and Drug Administration, Department of Health, Education, and Welfare, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Oral notices of participation will be accepted from persons who find insufficient the time available for submitting a written notice.

For further information or to give a notice of appearance orally, contact: Robert Nelson, Bureau of Drugs (HFD-120), Food and Drug Administration, Department of Health Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3800.

Supplementary information:

TERMINOLOGY

In this notice, DPX, the abbreviation for the dextrorotatory insomer (dextropropoxyphene) to which is attributed the analgesic effect of propoxyphene, is used to denominate propoxyphene-containing products generally. In some instances, the notice clearly specifies individual drug products or groupings of drug products containing DPX (e.g., combination drugs, or the drugs in the hydrochloride or the napsylate salt forms).

BACKGROUND

Propoxyphene (NPX) hydrochloride alone and in combination with aspirin, phenacetin, and caffeine was first marketed in 1957 by Eli Lilly & Co. (hereinafter referred to as "Lilly"). Under the law applicable at that time, the drug products (Darvon, Darvon Compound, and Darvon Compound-65) were approved for marketing based solely on evidence of safety. When demonstration of efficacy became a requirement in 1962, DPX was among the drugs reviewed for FDA by the National Academy of Sciences/National Research Council (NAS/NRC). In the Federal Register of April 8, 1969 (34 FR 6264), FDA announced the conclusion that DPX products (with the exception of the 32-milligram (mg) dose of propoxyphene hydrochloride) were effective "for the relief of mild to moderate pain."

In 1972, because of misleading claims made by Lilly, FDA required the firm to issue the following statements to physicians in a "Dear Doctor" letter: "There is no substantial evidence to demonstrate that 65 milligrams of Darvon is more effective than 650 milligrams of aspirin (two 5-grain tablets), and the preponderance of evidence indicates that it may be somewhat less effective. The preponderance of evidence indicates that Darvon is somewhat less potent than codeine. The best available evidence is that Darvon is approximately two-thirds as potent as codeine. Furthermore, there is no substantial evidence that, when administered at equianalgesic doses, Darvon produces a lower incidence of side effects than codeine."

In the Federal Register of December 27, 1972, (37 FR 28526) FDA announced a change in the labeling requirements for these products and acknowledged the limited effectiveness of the 32-mg dose of DPX hydrochloride in that: "recent studies have shown that this dose does have an analgesic effect in a certain fraction of the population with mild to moderate pain. While 32 milligrams of proproxyphene is a weak analgesic dose, only the physician attending a par-

ticular patient can determine by titrating the dose whether that individual patient is one of the minority who will respond adequately to the 32-milligram dose, or is one of the majority who will require at least 65 milligrams to achieve adequate analgesia."

Because of the abuse potential of DPX-containing products, they were placed in Schedule IV of the Controlled Substances Act in 1977. In an April 7, 1978 Federal Register notice (43 FR 14739), FDA revised labeling requirements to add warnings on adverse reactions; warnings on interaction with alcohol, tranquilizers, sedative/hypnotics, and other central nervous system depressants; and information on management of overdosage.

In the early 1970's after approval of new drug applications (NDA's) based on bioavailability studies, Lilly marketed new products containing the napsylate salt of DPX, either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA).

Since then, more than 50 abbreviated new drug applications (ANDA's) have been submitted and approved for over 30 "me-too" manufacturers of DPX products marketed under a variety of trade names.

Through the years, DPX-contining products have become among the most frequently prescribed prescription drugs in the United States. They peaked in popularity from 1973 to 1975, when retail prescriptions totalled over 39 million annually. While the total number of prescriptions has declined in recent years (total for 1978 is 31 million), DPX products are still very popular. among the 200 most prescribed drugs for the years 1972 through 1977 is shown in Table 1.

TABLE 1.—RANK AMONG THE TOP 200 MOST PRESCRIBED DRUGS [1]

	1972	1973	1974	1975	1976	1977
Darvocet-N (propoxyphene napsyiate with acetaminophen)		87	24	20	18	[2] 12
Darvon 32 mg and 65 mg (propoxyphene hydrochloride)	35	47	68	71	78	93
Darvon Compound-65 APC	2	3	3	6	15	20

[1] Source: National Prescription Audit, IMS America.

[2] Darvocet-N was divided into two groups (50 and 100) for the year 1977 only. The 1977 rank for Darvocet-N 100 was 18; for Darvocet-N 50 it was 169. The 1977 ranking of 12 for Darvocet-N was derived by aggregating data for Darvocet-N 50 and 100, in order to simplify the comparison with previous years.

RECENT DEVELOPMENTS

During the 1970's clinical experience with DPX and publication of additional studies on the drug have given rise to some questions about its safety and efficacy. The reservations that FDA expressed in requiring certain labeling changes, described above, exemplify one result of such developments; another is the Drug Enforcement Administration's placement of DPX products in Schedule IV of the Controlled Substances Act.

On November 21, 1978, the Secretary of Health, Education, and Welfare was petitioned by the Health Research Group (HRG), Washington, D.C., to suspend approval of the NDA's for DPX-containing products under section 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), on the ground that the continued marketing of these drugs represents an imminent hazard to the public health. Alternatively, HRG requested that if the Secretary did not suspend approval of the NDA's, he would support HRG's petition to DEA that DPX be rescheduled as a Schedule II narcotic under the Controlled Substances Act (Ref. 1).

In response to the request of the Secretary for recommendations concerning these issues, FDA reviewed the following: Data cited by HRG; other available reports of studies on DPX in the scientific literature; information available from the Drug Enforcement Administration's Drug Abuse Warning Network (DAWN); data submitted by Lilly on fatalities resulting from DPX products; information presented before the Monopoly and Anticompetitive Activities Subcommittee of the Select Committee on Small Business, U.S. Senate, on January 31, February 1 and 5, 1979; and information considered at FDA's Drug Abuse Advisory Committee meeting on February 13, 1979.

On February 15, the Secretary announced his decision that evidence currently available does not warrant his invoking the imminent hazard provision of the Act. However, he directed FDA to take several specific actions to warn the public

of the nature and degree of risk now known to be associated with DPX use and abuse. In addition, the Secretary ordered FDA to hold a public hearing on the effectiveness, modes of use, and safety of DPX, and to conduct and complete a comprehensive study of the scientific data on DPX.

Highlights of material being studied by FDA are summarized in the following sections on "efficacy studies" and "safety".

EFFICACY STUDIES

Propoxyphene

1. *Early studies on DPX seemed to establish that the drug was an effective, though mild, analgesic.*—This was demonstrated by the conclusion of the NAS/NRC Panel on Drugs for Relief of Pain (Ref. 2). The chairman of the panel was Louis Lasagna, M.D., and expert in the field of clinical pharmacology and analgesia. William T. Beaver, M.D., a member of the panel and also an expert in the field of analgesia, concluded as follows in 1966: "In summary, dextropropoxyphene is a mild oral analgesic which is of questionable efficacy in doses lower than 65 milligrams. The drug is definitely less potent than codeine, the best available estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately ½ to ⅔ as potent as the latter drug. Likewise, dextropropoxyphene in 32 milligram to 65 milligram doses is certainly no more, and possibly less, effective than the usually used doses of aspirin or A.P.C." (Ref. 3).

2. *Further reviews of 1970 and 1972 confirmed previous views of DPX as effective for mild to moderate pain.* The methodology for the clinical assay of analgesic efficacy was less sophisticated at that time, however, and many of the early studies would not meet today's criterial as adequate and well controlled (21 CFR 314.111). Thus, in a review paper published in 1970 by Miller et al., less than 10 percent of the published reports of DPX hydrochloride that were reviewed consisted of double-blind placebo comparisons. Miller cited 9 of 18 placebo-controlled trials in which DPX was more effective than placebo and concluded that "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" (Ref. 4). Prior to the 1972 labelling changes. Dr. Beaver again reviewed for FDA the published scientific literature on DPX products and concluded that they were effective (Ref. 5).

At the time of these reviews, it appeared that most of the studies that did not demonstrate efficacy showed significant methodological problems or lack of assay sensitivity in that they were unable to distinguish between a codeine or aspirin "standard" and placebo. However, some recent studies have *not* shown these problems; they appear adequate and well controlled and repeatedly demonstrate the efficacy of other analgesics but have not done so with DPX.

3. *Three recent "negative" studies are cited in the HRG petition.*—The first is a 1972 study by Moertel et al., in which DPX was compared to other marketed analgesics and placebo in a single-dose trail in cancer patients. DPX, ethoheptazine, and promazine were not superior to placebo in the relief of pain. Aspirin (650 mg) was found to be the most effective agent, followed by pentazocine, acetaminophen, phenacetin, mefenamic acid, and codeine (Ref. 6).

Hopkinson et al. in a study reported in 1973, compared single doses of DPX hydrochloride (65 mg), acetaminophen (650 mg), DPX plus acetaminophen, and placebo in 200 patients with postepisiotomy pain and found that DPX was statistically no better than placebo in the relief of pain (Ref. 7).

Gruber, in a two-dose study in 46 patients, compared DPX napsylate (50 to 100 mg) to codeine (30 or 60Mg) and placebo. He found that although there was no measurable difference betweeen either active drug and placebo after the first dose, both drugs were superior in effect to placebo after the second dose (the drugs were not significantly different from each other) (Ref. 8).

4. *Not all recent reports are negative.*—A 1978 study by Sunshine et al. found DPX napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was slightly better than placebo, but the usual dose (100 mg) was not tested (Ref. 9). These reports reinforce the conclusions of Beaver in 1966 that the results of DPX efficacy studies "of apparently suitable design . . . are to a degree contradictory" (Ref. 3).

In a second review by Miller in 1977, three studies showed DPX to be no more effective than placebo, and in five other DPX was as effective as the standard

agent (Ref. 10). Beaver, in his recent Senate testimony (Ref. 11), note five recent positive studies (Baptisti, 1971; Berry, 1975; Winter, 1973; Young, 1978: and Wang, 1974).

Propoxyphene combinations

1. *For DPX combinations,* the efficacy issue is not whether they are effective per se since it is presumed they are at least as effective as the aspirin, acetaminophen, or APC component. Rather, the question is whether the DPX component contributes to the efficacy of the combination, as required by 21 CFR 300.50 (fixed combination prescription drugs).

2. *A 1971 review of studies* by Beaver contains one of the earlier views on the efficacy of DPX combinations. Beaver noted several positive studies (Brooke and Brooke, 1966; Gruber, 1962; Marrs. 1959) and concluded that "although the design and results of available studies comparing combinations of DPX and either aspirin or APC with their individual constituents leave much to be desired, there is substantial evidence that these combinations are more effective than their constituents administered separately" (Ref. 5).

3. *Three references are cited in the HRG petition:* Hopkinson et al. found that there was no significant difference between the efficacy of acetaminophen alone and that of acetaminophen in combination with DPX. (Acetaminophen alone or in combination with DPX was significantly more effective than DPX alone and placebo (Ref. 7)).

In a 1974 study of the efficacy of combination drugs containing aspirin, Moertel et al. found that DPX napsylate (100 mg) did not significantly increase the analgesic effect of 650 mg aspirin. (Three compounds, codeine, pentazocine, and oxycodone, did significantly increase the aspirin's analgesic effect; in addition to DPX napsylate, other substances that did not increase aspirin's analgesic effect were ethoheptazine, pentobarbital, and caffeine.) Moertel noted the "conflicting evidence in the literature regarding the effectiveness of propoxyphene" and concluded that "it remains to be clearly established that its popularity reflects true analgesic effectiveness" (Ref. 12).

On the other hand, Bauer et al. in 1974 reported the results of a study that did show that the addition of DPX to the anti-inflammatory analgesics (aspirin at three different doses and penacetin at three doses, plus or minus caffeine) produced a significant increase in analgesia. This was a factorial efficacy study of DPX, aspirin, and APC in 610 subjects by two investigators in two separate institutions. DPX was never tested alone, however, and the increased analgesia of the DPX combinations was accompanied by a significant increase in side effects. The authors noted that the aspirin-containing products were packaged improperly, but the possible loss of efficacy due to pharmaceutical instability was not tested by chemical analyses. This positive multifactorial study of the contribution of DPX to the efficacy of DPX combinations is large, contains 10 medication test groups but no placebo control, and has other methodological weaknesses. According to the authors, the data obtained at the two institutions "differed significantly and possibly should not be pooled". Nevertheless, the results were pooled and no assessment of individual studies is possible. Moreover, the most effective treatment group used DPX napsylate at 200 mg (twice the recommended dose). There was also a failure of the relative potency assay assessment for the different doses of aspirin, thought possibly due to the instability of the aspirin due to the defective packaging (Ref. 13).

4. *A review by Miller* in 1977 found that only the Bauer study showed a contribution of DPX to the DPX–APC combinations. As noted above, however, the problems of design and analysis in the Bauer study are substantial. Miller concluded that in the interim since his 1970 review, no newly published studies showed that DPX contributed significantly to the efficacy of DPX-aspirin or DPX-acetminophen combinations. In fact, he found that the only recent well-designed studies (Moertel and Hopkinson) showed no contribution of DPX to the efficacy or the combinations of DPX to the efficacy of the combinations (Ref. 10).

SAFETY

Concerns about the safety of DPX center primarily upon its relationship to the deaths of DPX users, rather than upon side effects associated with the drug, which have been thought to be relatively minimal when the drug is used as directed at the recommended doses. Concerning side effects, for example, Miller

and Greenblatt reported that adverse reactions to DPX in hospitalized patients were infrenquent and mild. The adverse reactions, although qualitatively similar, occurred less often than with codeine and other analgesics used in hospitalized patients. Standard tolerance studies in volunteers revealed no significant differences between DPX and placebo (Ref. 14). In contrast, Goodman and Gilman state that in doses equianalgesic to codeine it is likely that the incidence of side effects would be similar to those of codeine (Ref. 15).

Reports of deaths in connection with DPX use have frequently relied upon statistics received from the Drug Abuse Warning Network (DAWN) system. This system, from which data are cited in the HRG petition, is a large-scale data-collecting system, initiated in September of 1972 and operated for the Federal Government on contract by IMS America, Ambler, PA DAWN collects data from over twenty large metropolitan areas in the continental United States and tabulates them as the number of "mentions" of a drug after persons have been in contact with or treated by one or three types of facilities: emergency rooms in non-Federal short-term general hospitals (as defined by the American Hospital Association), offices of medical examiners or coroners, and crisis intervention centers. An "episode" is either a drug-related death or a drug-related visit to an emergency room, and a "mention" is the report of a drug associated with an episode. If three drugs were reported for one episode, for example, three drug mentions would be recorded. Certain analytical problems may arise because of factors such as the lack of precision in reporting (e.g. the names of the drugs involved may be given to an emergency room in jargon that makes it impossible to assign the mention precisely to a particular drug or drugs) and the limitations in the system itself (e.g. the number and characteristics of the facilities reporting to the DAWN system have not remained constant). Despite these problems, DAWN data are regarded as useful in identifying trends or indicating the development of drug problems. Although the data are not measures of the absolute size of a drug problem, they illuminate aspects of the nature of such a problem, and are helpful in making comparisons among drugs. The DAWN data which follow include only mentions from emergency rooms and medical examiners or coroners, excluding crisis intervention center reports. Although for many analyses it is appropriate to limit the data for a given period to that reviewed from consistent reporters, that was not done in this case because of the importance of not omitting any useful information.

Table 2 compares DAWN data on coroners' reports of deaths (associated with DPX alone or in conjunction with other factors) with data on emergency room visits. Although there is a slight increase in deaths in 1977 compared with the previous 3 years, this difference is of questionable significance. In most instances, other substances (e.g. tranquilizers) are also implicated in the deaths.

TABLE 2.—CORONERS' REPORTS AND EMERGENCY ROOM VISITS IN WHICH PROPOXYPHENE (DPX) IS MENTIONED[1]

Year	Coroners' reports			Emergency room visits		
	Total	DPX only	Percent	Total	DPX only	Percent
1974	574	155	27.0	3,565	1,352	37.9
1975	582	137	23.5	3,508	1,259	35.9
1976	477	116	24.3	3,572	1,318	36.9
1977	531	179	33.7	3,434	1,292	37.6

[1] Source: DAWN data, IMS America.

Comparisons on safety of DPX and other drugs are shown in Tables 3 and 4. Not only are total DAWN mentions (coroner and emergency room) for the drugs provided, but also comparisons indicating the ratios of DPX-associated deaths to prescriptions dispensed. The data indicate that DPX is the most frequently mentioned single drug on coroner's reports. However, the ratio of DPX-associated deaths (coroners' mentions) to dispensed prescriptions is lower than that for the barbiturates, ethchlorvynol, glutethimide, methaqualone, amitriptycline, doxepin, and pentazocine, as shown in Table 3. When comparisons are made according to drug groupings, as in Table 4, the propoxyphene ratio is considerably lower than that for three other drug groups ("barbiturates," "other sedative/hypnotics," and "antidepressants").

TABLE 3.—COMPARISON OF PROPOXYPHENE WITH OTHER DRUGS; ASSOCIATIONS WITH EMERGENCY ROOM (ER) MENTIONS AND CORONER MENTIONS (DEATHS), 1977 [1]

Drug	Total prescriptions (millions)	Emergency room mentions	Coroner mentions	Coroner mentions: Coroner mentions/ emergency room mentions	Coroner mentions: Coroner mentions/ million prescriptions	Coroner mentions: Rank: Coroner mentions/ million prescriptions
Barbiturates:						
Secobarbital	1.2	2,457	350	0.14	292	3
Pentobarbital	1.3	946	272	.29	209	4
Secobarb/amobarb	1.0	3,093	326	.11	326	2
Amobarbital	.3	130	123	.95	410	1
Phenobarbital	7.8	2,989	254	.08	32.6	9
Benzodiazepines:						
Diazepam	53.6	21,678	418	.02	7.8	18
Chlordiazepoxide	13.0	3,411	54	.02	4.2	22
Flurazepam	13.6	4,643	80	.02	5.9	19
Other sedative/hypnotics:						
Meprobamate	8.2	1,238	95	.08	11.6	16
Methaqualone	1.0	2,405	62	.03	62.0	6
Ethchlorvynol	1.7	2,202	135	.06	79.4	5
Glutethimide	1.8	639	94	.15	52.2	7
Chloral hydrate	2.0	618	35	.06	17.5	13
Tranquilizers/antidepressants:						
Trifluoperazine	3.0	1,072	6	.01	2.0	24
Thioridazine	6.8	2,175	74	.03	10.9	17
Chlorpromazine	4.7	2,404	64	.03	13.6	15
Amtriiptyline	9.0	3,281	386	.12	42.9	8
Imipramine	4.6	921	74	.08	16.1	14
Doxepin	4.1	1,397	104	.07	25.4	10
Haloperidol	1.6	1,058	3	.01	1.9	25
Analgesics:						
Morphine	.6	134	0			
Codeine and codeine compounds	49.8	3,597	274	.08	5.5	20
Fiorinal	7.5	1,204	0			
Fiorinal with codeine	2.3	130	1	.01	.43	26
Pentazocine	3.5	1,079	71	.07	20.3	11
Pentazocine compound	.7	4	0			
Aspirin	NA	7,184	156	.02		
Acetaminophen	NA	2,559	77	.03		
Propoxyphene	33.5	4,179	607	.15	18.1	12
Other:						
Diphenhydramine	10.8	1,113	23	.02	2.1	23
Diphenylhydantoin	8.6	2,271	41	.02	4.9	21
Methapyrilene/scopolamine (OTC)	NA	1,725	1			

[1] Source: DAWN and NPA data.

TABLE 4.—COMPARISON OF PROPOXYPHENE WITH OTHER DRUG GROUPINGS; ASSOCIATIONS WITH DEATHS, 1977 [1]

Drug group	Total prescriptions	Coroner mentions	Coroner mentions/ million prescriptions	Group rank
Barbiturates [2] (Secobarbital, pentobarbital, amobarbital, and seco/amobarbital.)	3.8	1,071	282.0	1
Other sedative/hypnotics [2] (Methaqualone, ethchlorvynol, glutethimide, and chloral hydrate.)	6.5	326	50.0	2
Benzodiaepines (Diazepam, flurazepam, and chlordiazepoxide.)	80.2	552	7.0	6
Major tranquilizers (Chlorpromazine, thioridazine, trifluoperazine, and haloperidol.)	16.1	147	9.0	5
Antidepressants (Amitriptyline, imipramine, and doxepin.)	17.7	564	32.0	3
Other common prescription analgesics (Fiorinal with or without codeine, codeine with or without other analgesics, and pentazocine with or without other analgesics.)	63.8	346	5.0	7
Propoxyphene with or without other analgesics	33.5	607	18.1	4

[1] Source: DAWN and NPA data.
[2] Phenobarbital and meprobamate were intentionally excluded since their predominant use, as anticonvulsant and "muscle relaxant," respectively, differs from other drugs in the same pharmacologic category.

The circumstances under which the DPX-related deaths occurred are a matter of special interest. Particularly relevant are considerations such as whether other drugs or alcohol were also involved, whether an overdose of DPX was taken, and to what extent the deaths were intentional. Although it is impossible to determine precisely the answers to such questions, some generalizations can be made from available data.

1. DPX is a common cause of drug-associated death. These cases involve both suicide and accidents, but a majority of the deaths appear to be intentional. Thus, a tabulation of the 72 DPX-related deaths reported in 1971–1975 by the San Francisco Coroner's Office indicates that 58 percent of them were suicides (this compares with 10 codeine-related deaths, of which 50 percent were suicides). Analysis of data available from different sources, as shown in Table 5, supports the hypothesis that a substantial proportion of DPX deaths are the result of use by those in younger age groups, for suicidal purposes or associated with abuse. Thus, 8–22 percent of the deaths are in the 10–19 age group, which accounts for only 7 percent of the prescriptions; 48–58 percent of the deaths are in the 20–39 age group with approximately 30 percent of the DPX prescriptions. Regardless of age considerations, however, it is apparent that DPX is one of the prescription drugs most frequently associated with suicide and accidental deaths, ranking behind only the barbiturates as a group in total number and behind only barbiturates, other sedative-hypnotics and antidepressants in deaths per million prescriptions dispensed (Table 4).

TABLE 5.—PROPOXYPHENE: REPORTED PRESCRIBING, EMERGENCY ROOM VISITS, AND ASSOCIATED DEATHS, BY AGE

Category	Percentages by age groups						
	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 and over
Reported prescribing of propoxyphene [1]	1	7	[2] 30		[3] 26		35
Emergency room visits for suicide gestures [4] (Total equals 505.)		37	40	11	6	4	1
DAWN emergency room data [5] (Total equals 16, 113.)		24	40	19	10	[6] 6	
Deaths:							
FDA: Probable suicides reported [7] (total equals 173, 50 percent male, 50 percent female)		22	37	20	14	8	
FDA: Probable accidental deaths [7] (total equals 48, 40 percent male, 60 percent female)	13	13	34	17	6	2	
Finkle data: Propoxyphene-associated deaths [8] (total equals 1,022, 45 percent male, 55 percent female)	2	12	27	21	20	11	8
DAWN medical examiner data [5] (total equals 1,964)		8	35	23	17	[6] 17	

[1] National Disease and Therapeutic Index, IMS America.
[2] This figure is for the age group 20 to 39.
[3] This figure is for the age group 40 to 59.
[4] FDA National Clearinghouse for Poison Control Centers.
[5] Drug Enforcement Administration, Drug Abuse Warning Network, January 1975 to August 1978.
[6] This figure is for the age group 50 and over.
[7] FDA spontaneous adverse reaction reporting program. (In 15 percent of the reports age was not reported.)
[8] Reference 17.

2. A majority of the DPX-related deaths appear to have occurred when DPX was taken in conjunction with alcohol or other drugs. Thus, information from various sources, shown in table 6, indicates that in about 12–28 percent of the deaths, DPX alone was involved; in the others alcohol and/or other drugs were also present.

TABLE 6.—DEATHS ASSOCIATED WITH PROPOXYPHENE (DPX)

Category	Source of data: Baselt et al.[1]	Hine et al.[2]	Finkle et al.[3]	FDA reports of accidental deaths[4]	DAWN medical examiner reports of accidental or unexpected deaths[5]: 1975	1976	1977
Total cases	29	72	1,022	48	229	187	179
Years involved	1973–74	1971–75	1972–75	1969–77	1975	1976	1977
Mean age	38	35	25	30			
Percent male	58	56	45	40			
Due to DPX alone:							
Number	8	14	244	15	56	27	29
Percent of total	28	19.6	24	27	24	12	16
Due to DPX and ethyl alcohol:							
Number	5	23	238	15	36	40	29
Percent of total	17	32	23	31	16	21	16
Due to DPX and other drug only:							
Number	8	17	349	10	101	87	79
Percent of total	28	23.6	34	21	44	47	44
Due to DPX and ethyl alcohol plus other drug(s):							
Number	8	18	191	6	32	26	28
Percent of total	28	25	18	12	14	14	16

[1] Reference 16.
[2] Reference 18.
[3] Reference 17.
[4] FDA spontaneous adverse reaction reporting program.
[5] Drug Enforcement Administration, Drug abuse Warning Network.

3. At present there is no clear evidence of deaths attributed to DPX products alone when taken in recommended doses and without alcohol or tranquilizers also being involved. There are, however, several "accidental" deaths that have occurred apparently as a result of the consumption of DPX in quantities only slightly in excess of recommended therapeutic dosage, usually combined with alcohol or tranquilizers or both. Dr. Larry Lewman, Multnomah County (Oregon) Medical Examiner, in testimony before the Senate Subcommittee cited previously in this notice, presented data in support of this possibility (Ref. 11). While reports such as this are very infrequent, given the wide availability of DPX, they raise concern that death of persons taking the drug at or near the recommended doses may be more common than is currently appreciated.

4. The mechanism of death in cases of DPX overdose is commonly attributed to respiratory depression, a typical action of narcotics. This theory is substantiated by a large number of case reports from a wide variety of sources. However, the possibility of a specific and primary cardiotoxic effect, independent of respiratory depression has been raised. The demonstration of dose-related progressive condition block appears clear in experimental animals, and in some patients with acutely toxic overdoses there are reported electrocardiographic (ECG) changes. This is not unexpected in view of the local anesthetic activity of both DPX and its primary metabolite norpropoxyphene. It has been postulated that, with chronic dosing, DPX accumulates to near toxic levels and adversely affects myocardial conduction, but this has not been the experience in heroin addicts on long-term, high-dose DPX napsylate maintenance. Moreover, when there are ECG changes in DPX overdoses and the CNS depressant effects are reversed by naloxone, the ECG changes rapidly revert to normal when respiration returns (or is mechanically supported) and acidosis is corrected. Therefore; the cardiac changes are most likely secondary to hypoxia rather than norpropoxyphene toxicity, which would take at least several hours to be reversible. Moreover, as shown in Table 5, only a small percentage of the deaths are in the over 60 age group which accounts for 35 percent of the reported prescribing. This population would be presumably more sensitive to any cardiovascular toxicity associated with DPX, but the paucity of deaths in this age group is notable. Cardiotoxicity at a therapeutic dose has not been observed.

5. DPX can produce psychological and physical dependence of the opiate type when taken for an extended period of time. It will substitute for other opiates in addicted persons, but only to a limited extent. Because of the abuse potential of DPX, it was placed in Schedule IV of the Controlled Substances Act. The

Health Research Group believes the restrictions of Schedule IV are not sufficient to protect the public from the dangers of DPX use and has proposed it be transferred to the most restricted control, Schedule II.

REFERENCES

The following items specifically cited in this notice, as well as a number of other items related to the DPX hearing, are on file and available for inspection in the office of the Hearing Clerk, at the address specified at the beginning of this notice.

1. Petition from Health Research Group, Washington, D.C., to Secretary J. Califano, November 21, 1978.

2. National Academy of Sciences/National Research Council; Report of Panel on Drugs for the Relief of Pain on Darvon Compound, NDA 10-996.

3. Beaver, W. T., "Mild Analgesics, A Review of Their Clinical Pharmacology (Part II)," *American Journal of Medical Science*, 25:576-599, 1966.

4. Miller, R. R., A. Feingold and J. Paxinos, "Propoxyphene Hydrochloride," *Journal of American Medicine*, 213(6):996-1006, 1970.

5. Beaver, W. T., Memorandum to Henry E. Simmons, Director, Bureau of Drugs, Food and Drug Administration, May 18, 1971.

6. Moertel, C. G., D. L. Ahmann, W. F. Taylor, and N. Schwartau, "A Comparative Evaluation of Marketed Analgesic Drugs," *The New England Journal of Medicine*, 286:813-15, 1972.

7. Hopkinson, J. H., IV, et al., "Acetaminophen Versus Propoxyphene Hydrochloride for Relief of Pain in Episiotomy Patients," *The Journal of Clinical Pharmacology*, 113:251-263, 1973.

8. Gruber, C. M., Jr., "Codeine and Propoxyphene in Postepisiotomy Pain," *The Journal of the American Medical Association*, 237: 2734-35, 1977.

9. Sunshine, A. J. Slafta and C. Gruber, Jr., "A Comparative Analgesic Study of Propoxyphene, Fenoprogen, the Combination of Propoxyphene and Fenoprofen, Aspirin, and Placebo," *The Journal of Clinical Pharamacology*, 18:556-563, 1978.

10. Miller, R. R., "Propoxyphene, A Review," *American Journal of Hospital Pharmacy*, 34:413-423, 1977.

11. Propoxyphene Hearings (January 31, February 1 and 5, 1979) of the Monopoly and Anticompetitive Activities Subcommittee of the Select Committee on Small Business, U.S. Senate.

12. Moertel, C. G., D. L. Ahmann, W. F. Taylor, and N. Schwartau, "Relief of Pain by Oral Medications," *The Journal of the American Medical Association*, 229(1):55-59, 1974.

13. Bauer, R. O., A. Baptisti, Jr., and C. M. Gruber, Jr., "Evaluation of Propoxyphene Napsylate Compound in Postpartum Uterine Cramping," *The Journal of Medicine*, 5:317-328, 1974.

14. Miller, R. and D. J. Greenblatt, "Drug Effects in Hospitalized Patients: Experiences of the Boston Collaborative Drug Surveillance Program, 1966-1975," John Wiley & Sons, New York, pp. 162-164, 1975.

15. Jaffe, J. H. and W. R. Martin, "Narcotic Analgesic and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, MacMillan Publishing Co., Inc., New York, pp. 270-271, 1975.

16. Baselt, R. C. and J. A. Wright, J. E. Turner, and R. H. Cravey, "Propoxyphene and Norpropoxyphene Tissue Concentrations in Fatalities Associated with Propoxyhene Hydrochloride and Propoxyphene Napsylate," *Archives of Toxicology*, 34:145-152, 1975.

17. Finkel, B. S., K. L. McCloskey, G. F. Kiplinger, and I. F. Bennett, "A National Assessment of Propoxyphene in Postmortem Medicolegal Investigation, 1972-1975," *Journal of Forensic Sciences*, 21(4):706-742, 1976.

18. Hine, C. H., J. A. Wright, D. J. Allison, B. G. Stephens, and A. Pasi, Analysis of Fatalities due to Acute Narcotism in a Major Urban Area (umpub.).

PUBLIC HEARINGS

The Food and Drug Administration announces that a public hearing will be held to obtain additional information and recommendations relevant to consideration of further regulatory actions on DPX-containing drug products. The

hearing is open to all interested persons. Participants are invited to comment on the material presented in this notice and to contribute any additional well-documented information that will be of use to the Commissioner in evaluating efficacy, assessing risks, and analyzing risk/benefit considerations associated with the use of DPX and DPX-containing combinations. Specifically, the objective of the hearing will be to gather evidence on the following issues:

1. Is there "new evidence of clinical experience, not contained in the NDA's or not available to the Food and Drug Administration until after such applications were approved, or are there tests by new methods, or tests by methods not deemed reasonably applicable when the applications were approved which when evaluated together with the evidence available when the applications were approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the applications were approved"? (21 CFR 314.115(b)(2)). Specifically, how many of the deaths associated with DPX are suicides; how many are accidents resulting from abuse or misuse; and how many are accidents resulting from normal use? Are there any deaths resulting from DPX taken at recommended doses, either alone or in combination with alcohol and other drugs? What are the blood levels of DPX and its major metalbolite, norpropoxyphene, that are associated with death, and what is the relationship of these levels to those observed when the drug is taken at recommended doses? What is the mechanism of death in these cases? Is it only respiratory depression, or is there a previously unrecognized effect on cardiac conduction? Are there differences in risk among DPX-containing salts and combinations?

2. Is there "lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof"? (21 CFR 314.115(b)(3)). Specifically, is there scientific evidence that DPX contributes to the analgesic effect of combination products containing aspirin, acetaminophen, or APC, as required by the FDA fixed-combination policy? (21 CFR 300.50(a)). Are there any differences in effectiveness or other benefits among particular salts or combinations of DPX?

In addition, the agency is interested in receiving testimony on whether additional regulatory action is needed at this time with respect to DPX-containing products. Such action could include, but is not necessarily limited to, removal of some or all of these products from the market, rescheduling under the Controlled Substances Act to Schedule III or II, the placing of new warnings in the labeling for physicians or a limitation in the labeling to use in patients who cannot tolerate other analgesics, and/or providing patients with warnings or other information. In a related, though separate, proceeding, the issue of whether DPX should be placed in Schedule II of the Controlled Substances Act, 21 U.S.C. 801 et seq. is being considered by the FDA's Drug Abuse Advisory Committee, which held an initial meeting on the subject on February 13, 1979 and will hold its second and final such meeting on April 17, 1979 to enable FDA to meet a June 1, 1979 deadline set by the Secretary of Health, Education, and Welfare for recommendations on scheduling of DPX. Because that issue is being fully considered in that particular context, it is requested that participants at this hearing not focus primarily on the scheduling issue.

The record of another related proceeding, the testimony at the propoxyphene hearings on January 31, February 1 and 5, 1979 of the Monopoly and Anticompetitive Activities Subcommittee of the Select Committee on Small Business of the U.S. Senate, is already the subject of review and study by FDA. For that reason, it will be unnecessary for participants to duplicate any of that testimony at this hearing.

The hearing will begin at 9 a.m. on April 6, 1979, in the Snow Room (Room 5051), HEW North Building, 330 Independence Ave., SW., Washington, D.C. The presiding officer will be Ronald Kartzinel, M.D., Ph. D., Director of the Division of Neuropharmacological Drug Products, Bureau of Drugs, FDA.

Persons wishing to comment or present views at the hearing must file by March 23, 1979, a written notice of participation under 21 CFR 15.21 with the Hearing Clerk (HFA-305). Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, MD 20857. The Envelope containing the notice should be prominently marked "Propoxyphene Hearing." The notice of participation should contain the following: Hearing Clerk Docket No. 77N-0266; the name, address and telephone number of the person desiring to make a statement; busi-

ness or professional affiliation, if any; the subject of the presentation; and the approximate amount of time being requested for the presentation.

A notice of participation may be telephoned to Mr. Robert Nelson, 301–443–3800 by persons who find there is insufficient time to submit the require information in written form.

Individuals and organizations with common interests are urged to consolidate or coordinate their presentations. The agency may require joint presentations by persons with common interests. It will allocate the time available for the hearing among the persons who properly file a notice of participation and will make a schedule of the hearing available to those persons. Persons may use their allotted time on any aspect of the proposed action, consistent with the conduct of a reasonable and orderly hearing. Formal written statements on the issues may be presented to the presiding officer on the day of the hearing for inclusion in the record. The time available for the hearing may make it impossible to accommodate all those desiring to appear. The Commissioner encourages those not appearing in person to submit their information in written form for inclusion in the administrative record of the drug.

The hearing will be open to the public. At the discretion of the presiding officer, and as time permits, any interested person in attendance may speak on matters relevant to the issue under consideration after scheduled parties have presented their views.

In order to permit time for all interested persons to submit data, information, or views, on the subject matter of the hearing, the administrative record of the public hearing will remain open for 45 days after the hearing is held.

Dated: February 26, 1979.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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