DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

MEMO TO FILE

NDA:	**10-997**
Drug:	**Darvon® (Propoxyphene HCl)**
Indication:	Analgesia
Sponsor:	Xanodyne Pharmaceuticals, Inc. (current holder of the Innovator's NDAs)
Related Sponsor Applications	NDAs 16-862, 17-122, ANDA 40-139, IND 70,462
Subject:	**Synopsis of Cardiac Inotropic Effects of Propoxyphene and Its Major Metabolite Norpropoxyphene, and the Possibility of Similar Effects by Alternative Opiate Analgesics if Propoxyphene was Discontinued**
Date of Memo:	January 25, 2010
Reviewer	L. Steven Leshin, DVM, PhD
Through	Adam Wasserman, PhD

Background

The issue of cardiotoxicity was raised in the Citizens Petition by Public Citizen Feb 28, 2006 (Docket 2006P-0090) and in a past petition by Public Citizen in Nov 1978. Refer to information in the Background Package to the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee of Jan 30, 2009. The FDA denied the petition's requested action to withdraw the approval of propoxyphene on July 7, 2009. Public Citizen then filed a Petition for Reconsideration of this decision on Aug 6, 2009 (Docket 2006P-0270), citing that the FDA action failed to address or incorporate a substantial amount of relevant information presented by Public Citizen at the Jan 30 , 2009 Advisory Committee Meeting.

The summary below is neither an exhaustive review of cardiotoxicity associated with the drugs in question, nor a response to points raised by Public Citizen in their 2006 and 2009 Petitions. Rather, the summary highlights what is known about relevant cardiotoxicity from nonclinical studies, since specific human information is not definitive although propoxyphene has been marketed since 1957. Additional information was presented in the Nonclinical Background summary for the Jan 30, 2009 Advisory Meeting (Appendix). In addition, since the possibility exists that the propoxyphene approval could be withdrawn and subsequently removed from the market, a brief summary of the cardiotoxicity of potential opiate analgesic alternative drugs is presented.

Propoxyphene and Norpropoxyphene

Dose-dependent negative inotropic effects of propoxyphene and norpropoxyphene were described with the in vitro studies of isolated Purkinje fibers of dogs and guinea pig atria (Figure 1, Holland and Steinberg, 1979), as well as isolated ventricular papillary muscle of cats (Figure 2, Amsterdam et al., 1981). In combination, an additive inhibitory effect on muscle tension was demonstrated when equal amounts of propoxyphene and norpropoxyphene were combined (Figure 3, Amsterdam et al., 1981).

Across studies, propoxyphene and norpropoxyphene have negative inotropic effects at concentrations of 10 μM (= 1 x 10^{-5} M). The effect of norpropoxyphene is slightly greater than that of propoxyphene, but there is an additive effect when both are tested together. It is unlikely there was sufficient time for significant endogenous metabolite production in these in vitro studies. Thus, either of these compounds could be detrimental to cardiac function at concentrations greater than therapeutic levels.

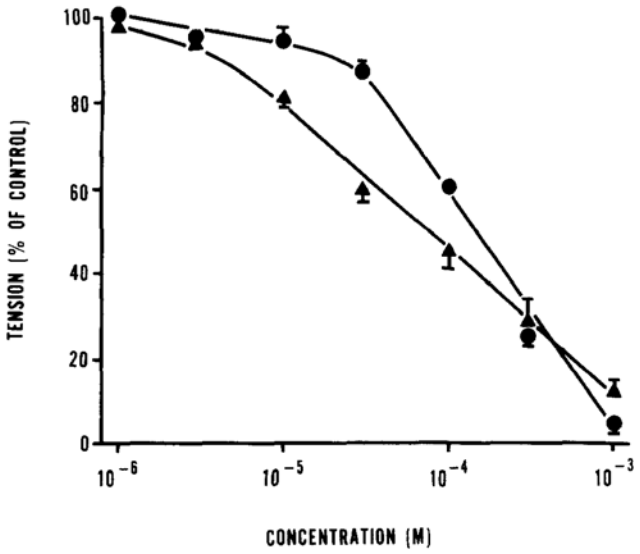

Figure 1: Concentration-dependent decrease (percentage control) in tension in guinea pig atria exposed to propoxyphene and norpropoxyphene. Inotropic studies were performed using isolated left atrial strips. All values are mean ± SE obtained from four to seven atria. For tension, the control values for propoxyphene were 0.33 ± 0.04 g and for norpropoxyphene were 0.53 ± 0.06 g. [From Holland and Steinberg 1979, Figure 4]

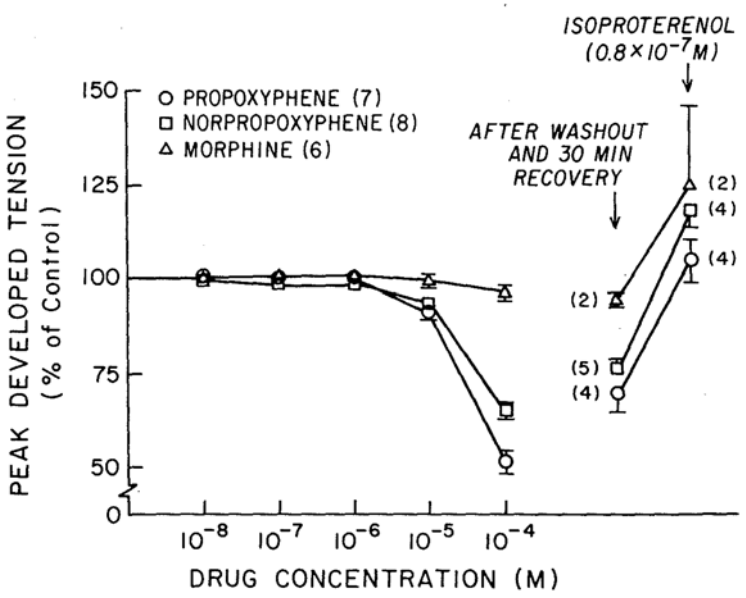

Figure 2: Dose-response curves demonstrating the effect of propoxyphene, norpropoxyphene, and morphine on maximal developed isometric tension of cat right ventricular papillary muscles. Each point represents group mean data; SEM is indicated for each point. The effects of drug removal (washout) and isoproterenol are indicated. Numbers in parentheses denote the number of muscles in each experimental group. [From Amsterdam et al, 1971, Figure 1]

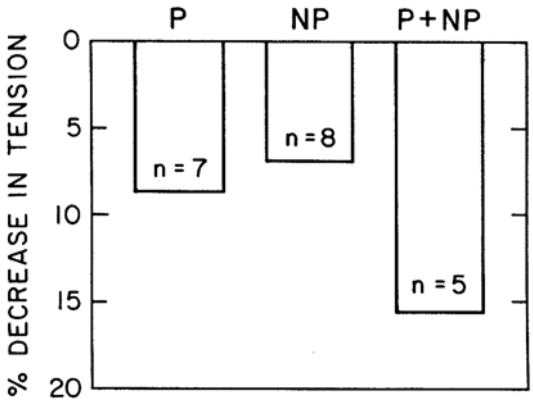

Figure 3: Decrease in maximal developed isometric tension of papillary muscles by 10^{-5}M concentrations of propoxyphene (P) and norpropoxyphene (NP), both together and separately. The vertical bars represent group mean data and the numbers in each bar indicate number of muscles in each group. [From Amsterdam et al, 1971, Figure 1]

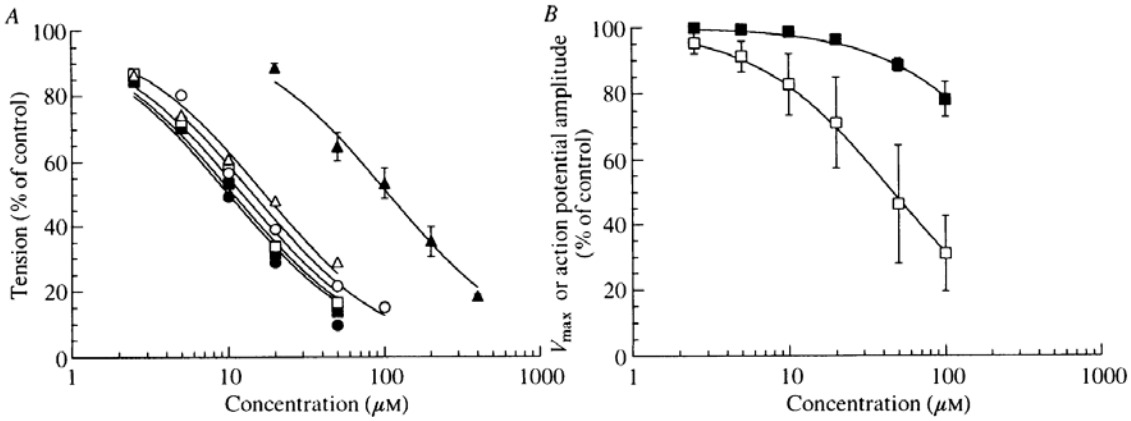

Figure 4: **A**, the effect of the opioids dextropropoxyphene (●), norpropoxyphene (■), methadone (□), pentazocine (○) and pethidine (▲) and quinidine (Δ) on isometric twitch tension. Values are means, and means ± S.E.M. for pethidine data. **B**, the effect of methadone on the maximum rate of depolarization (V_{max}) of the action potential (□) and the action potential amplitude (■). Values are means ± S.E.M. Curves are a fit of the data points to a first order reaction. [From Wu et al 1997, Figure 1, note that pethidine is another name for meperidine]

Due to the short time course of the in vitro studies, therapeutic Cmax values rather than AUC was used to compare the nonclinical and clinical drug concentrations to determine the nonclinical findings therapeutic relevance.

In the multiple dose study of Flanagan et al 1989, Co-Proxamol (a combination of dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg; 65 mg propoxyphene HCl per dose, was administered 3 times daily (195 mg/day) for a week. Since the multiple daily dosing in the US label allows for maximal human recommended dosing of 390 mg propoxyphene HCl or 600 mg propoxyphene napsylate (6 tablets/ day, once every 4 hours, 65 mg propoxyphene HCl, or 100 mg propoxyphene napsylate), one would expect greater AUC and possibly Cmax values with the greater dosing in the US. However, the Cmax obtained in healthy adults for the Flanagan et al 1989 study (Table 1) were similar to values in the recent IND 70,462 (Xanodyne Pharmaceuticals) clinical study XP20B-102 with the 100 mg tablet Darvocet-N treatment arm (propoxyphene napsylate with acetaminophen) in which 100 mg was administered every 4 hours for 56 doses (9 days). The average Cmax at the end of 9 days of dosing was 0.179 µg/mL (~0. 6 µM) for propoxyphene and 0.896 µg/mL (~3.0 µM) for norpropoxyphene. The napsylate salt has a slower absorption and longer overall time course than the HCl salt, so one would expect greater accumulation with the napsylate salt compared to the HCl salt given the same dosing frequency. Again the focus for this review is on Cmax rather than AUC, since the nonclinical in vitro studies were not conducted long enough for a relevant AUC comparison to human therapeutic dosing.

Table 1 Dextropropoxyphene and nordextropropoxyphene half-lives, maximum concentration (C_{max}), time to reach C_{max} (t_{max}) and dextropropoxyphene AUC (zero to infinity, single dose; zero to 8 h, multiple dose) after single and multiple dextropropoxyphene dosage (median, range)

	Dextropropoxyphene		*Nordextropropoxyphene*	
	Single dose	*Multiple dose*	*Single dose*	*Multiple dose*
Half-life (h)				
Young	13.0 (6.4–26.4)	22.0 (9.8–49.3)	22.2 (16.3–28.0)	22.1 (15.6–34.0)
Elderly	35.4 (1.9–86.8)	36.8 (17.4–110)	40.9 (28.4–106)	41.8 (32.9–62.8)
C_{max} ($\mu g\ l^{-1}$)				
Young	59 (26–90)	116 (51–214)	195 (151–229)	673 (477–839)
Elderly	156 (39–366)	239 (151–509)	193 (112–283)	1100 (775–1500)
t_{max} (h)				
Young	2.0 (2.0–3.0)	2.0 (2.0–5.0)	2.0 (2.0–5.0)	2.0 (2.0–12)
Elderly	1.5 (1.0–5.0)	2.0 (1.0–3.0)	2.0 (2.0–9.0)	2.8 (2.0–7.0)
AUC ($\mu g\ l^{-1}\ h$)				
Young	509 (217–1309)	731 (163–1420)		
Elderly	1402 (177–3976)	1155 (467–2664)		

Finkle et al (1981) provided concentrations of propoxyphene and norpropoxyphene from medical examiner records of subjects whom accidently or intentionally overdosed only from propoxyphene (117 cases). The range of propoxyphene and norpropoxyphene concentrations varied widely, and the therapeutic range described above is in the lower part of the scatterplot points. There were deaths within this therapeutic range. Despite the postmortem problems in assessing the timing and possible concentrations associated with the time of death, there did not appear to be any identifiable lethal threshold, since there was a substantial overlap in concentration of propoxyphene and norpropoxyphene in those that recovered and those that died regardless of the attempts of life-saving therapeutic treatment.

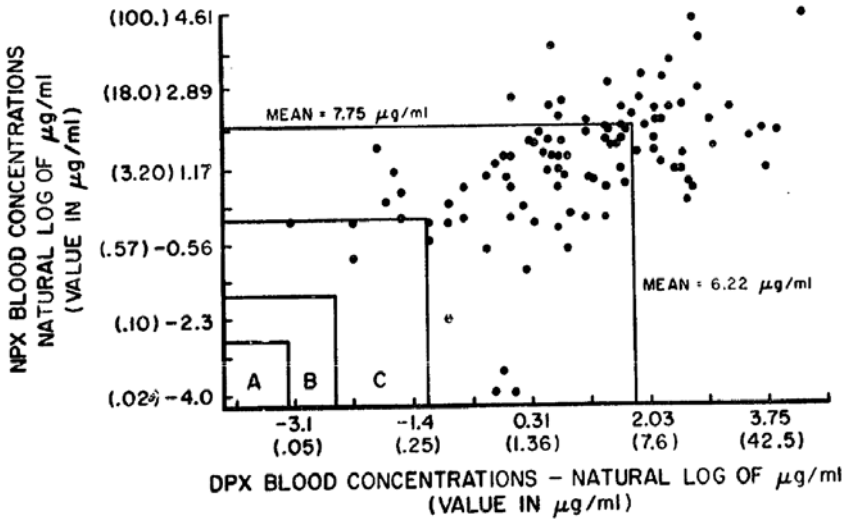

Figure 5: Propoxyphene (DPX) and Norpropoxyphene (NPX) blood concentrations for all cases involving propoxyphene alone (117 cases) [From Finkle et al 1981, Figure 10]

Thus, based on the available pharmacokinetic data (without consideration of tissue concentrations of drug and its impact on tissue function, and differences in free and protein-bound drug) sub-maximal dosing of propoxyphene in otherwise healthy patients would not be expected to reach concentrations of propoxyphene or norpropoxyphene that cause negative inotropic effects based on the nonclinical studies (NOAEL 1 μM, AEL = 10 μM). However, with maximal dosing, drug levels are attained that provided human safety margins between 0 and 2 for the non-clinically identified cardiotoxicities. In special populations such as the elderly, at the maximal recommended dosing, propoxyphene and norpropoxyphene attain levels at which negative inotropic effects were beginning to become evident in the nonclinical studies. The negative inotropic effects would be due to an additive effect of both propoxyphene and norpropoxyphene. Therefore, exceeding the therapeutic range by a small amount could readily put patients within the expected cardiotoxic drug concentration resulting in mortality as indicated in the human accidental and intentional overdose data.

Opiate Drugs

Opiate analgesics NSAIDs are possible alternative analgesic treatments if propoxyphene drugs were determined to be unsafe. Methadone is also the only opiate in which cardiac conduction effects (prolonged QT interval) are noted in the label.

> from Methadone label Nov 2006, NDA 6134 Dolophine HCl:
> Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of

> methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

The conduction properties of propoxyphene were described in the Nonclinical Background summary for the Jan 30, 2009 Advisory Meeting (Appendix). Based on human case reports, QRS widening is more common with propoxyphene than QT prolongation. Based on pharmacokinetic data within the product labels, methadone has the highest average Cmax of the opiate drugs and is similar to that of propoxyphene. The opiate pharmacokinetic data presented in Table 2 indicates the Cmax of methadone is 10-fold greater than morphine and oxycodone (methadone 3.63 μM > tramadol 1.97 μM > oxycodone 0.31 μM ≈ morphine 0.27 μM). Except for methadone, the opiates morphine, meperidine, fentanyl, pentazocine, and perhaps tramadol exhibit negative inotropic effect on cardiac muscle at doses of 10 or 100 μM which is 10- to 1000-fold greater than average Cmax values indicated in labels for these drugs (Figure 6, Rendig et al 1980; Figure 7, Motomura et al 1984; Table 3, Stauer 1972). The maximal clinical concentrations of these opiate drugs are probably underestimated, since the average Cmax was used and the dose and dosing regimen was not always indicated in the label prescribing information.

TABLE 2: HUMAN PHARMACOKINETICS: Cmax of oral analgesic opiates

Generic name (Brand names, not all listed)	**Oral Dosing Cmax (ng/mL)** (SD = single dose, MD = multiple dose)	**Mol. Weight**	**Source of Cmax data**
Buprenorphine (Subutex)	5.95 ± (38%-CV), SD	467.6	NDA 20732, label of Oct 2002
Butorphanol (Stadol)		327.5	no label info
Codeine	no PK info	317.4	
Hydrocodone/acetaminophen (Norco, Vicodin, Lortab)	23.6 ± 5.2 ng/mL, SD	380.9	ANDA 89736, label of Dec 2006
Fentanyl **(**Sublimaze; Actiq, Buccal, Duragesic)		336.5	
Hydromorphone (Dilaudid)	5.5 ± (33%-CV), SD	321.8	NDA 19892, label of Nov 2007
Levorphanol (Levo-Dromoran)		443.5	NDA 8720, no label info
Meperidine (Demerol)	no PK info	283.8	NDA 5010, label of March 2009
Methadone (Dolophine)	1255 ng/mL, MD **(~ 3.63 μM)**	345.9	NDA 6134, label of Nov 2006
Note: Methadone is the only opiate with specific cardiac conduction information in the label			
Morphine	78 ng/mL, qid, MD **(~ 0.27 μM)**	285.3	NDA 22207, label of March 2008

Oxycodone **(**OxyContin**)** **Oxycodone/acetaminophen** (Percocet, Tylox) **Oxycodone/aspirin** (Percodan)	98 ± (32%-CV), SD **(~ 0.31 µM)**	315.4	NDA 20553, label of Sept 2009
Oxymorphone (Opana ER)	4.5 ± 2, bid, MD 2.6 ± 1.6, SD	337.8	NDA 21610, label of Feb 2008
Pentazocine (Talwin)		285.4	no label info injectable NDA 16194 , other forms are tablets with aspirin, acetaminophen, naloxone
Tramadol (Ultram)	592 ± (30%-CV),qid, MD **(~ 1.97 µM)** 1308 ± (25%-CV), SD	299.8	healthy adults, Ultram NDA 21281 label Sept 2009

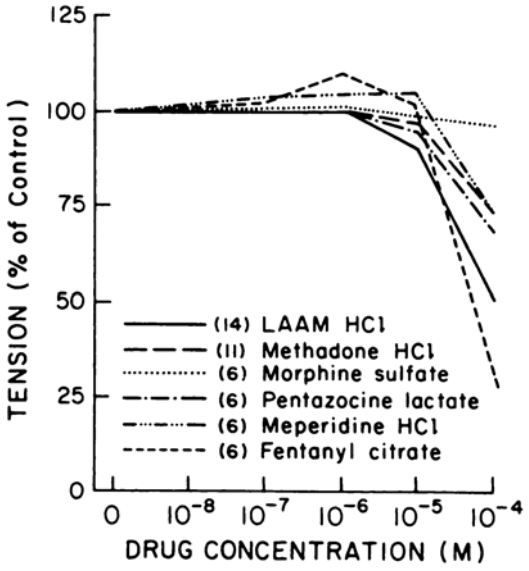

Figure 6: Dose-response curves showing the effects of six narcotic analgesics on peak developed isometric tension (T) in the cat right ventricular papillary muscle. For each drug, the average value of T at each of five narcotic concentrations is expressed as a percentage of the prenarcotic control T. The number of muscles studied for each drug is given in parentheses. [From Rendig et al 1980, Figure 1]

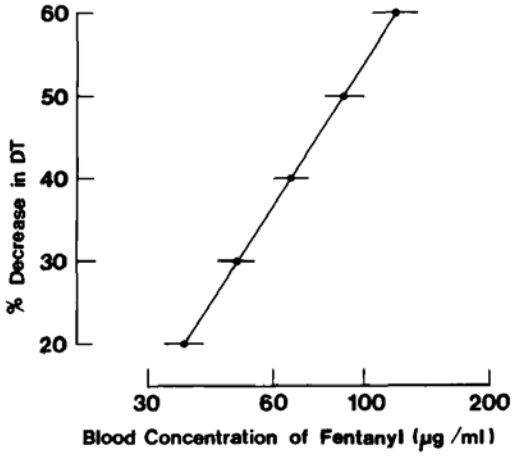

Figure 7: Fentanyl concentration-effect curve in the absence of nitrous oxide. Ordinate, decrease of the developed tension of the papillary muscle. Abscissa, blood concentration of fentanyl. [From Motomura et al 1984, Figure 2]

Table 3: Equianalgesic potencies of the Four Analgesics Investigated Related to 50 Per Cent Depression of Contractility*

	Equianalgesic Doses		Bath Concentrations that Produced 50 Per Cent Depression of Contractility (μg/ml)†	Relative Contractile Depressant Potencies
	mg	Potency		
Morphine	10	1	2,000	1
Meperidine	70	0.1–0.2	100	100–200
Fentanyl	0.1–0.2	50–100	10	2–4
Piritramide	5–10		1,000	1–2

* Equianalgesic potencies have been estimated in accordance with the equianalgesic doses (mg). Estimations are referred to the potency of an equalanalgesic dose of morphine (=1). Note the similar relations between contractile and the analgesic effects of morphine, fentanyl, and piritramide, whereas an equianalgesic dose of meperidine produces an approximately 100-200-fold decrease in contractility.

† Related to 50 per cent reduction of dl/dt_{max}.

[From Stauer 1972, Table 1]

More recent research indicated that opioid induced negative inotropic effects in the isolated human atria tissue was not mediated by mu, delta or kappa receptors (Llobell and Laorden 1995). In a hamster model of the cardiomyopathy, delta and kappa opioid receptors mediated negative inotropic responses of isolated ventricular muscle through kappa receptor activation of pertussis toxin-sensitive G-protein (Bolte et al 2009). However most opiates used for therapeutic pain relief have very little kappa receptor activity, rather most opiate analgesics have mu-receptor agonist activity or a combination of mu- and delta-receptor agonist activity.

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Llobell F, Laorden ML. 1995. Characterization of the Opioid receptor Subtypes Mediating the Negative Inotropic Effects of DAMGO, DPDPE and U-50,488H in isolated human right atria strips. Neuropeptides 29:115-119.

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APPENDIX

BACKGROUND FOR THE PROPOXYPHENE ADVISORY COMMITTEE

NONCLINICAL SAFETY

Introduction

This presentation will cover nonclinical pharmacology and toxicology findings that are relevant to therapeutic and supratherapeutic (overdose) use of propoxyphene. Since the majority of nonclinical studies were conducted in the 1950's and 1960's and have since been published, emphasis will be on information obtained since the last propoxyphene Advisory Committee meeting in 1979 which was held in response to a 1978 Petition (also from Public Citizen). It was claimed then that the major metabolite, norpropoxyphene, was instrumental in causing cardiotoxicity and this issue is a critical safety element raised in the current 2006 Petition. Therefore, this presentation will address new information on propoxyphene pharmacology and nonclinical data pertaining to cardiac toxicity.

Pharmacology

Propoxyphene

Propoxyphene is a synthetic diphenyl heptane analgesic with structural similarity to methadone (Appendix, Figure 1). There are four propoxyphene stereoisomers. The alpha dextro-propoxyphene isomer possesses analgesic activity (Gruber et al 1955) and was patented in 1955 by Eli Lilly, marketed beginning in 1957, and is the propoxyphene form which is the subject of this meeting. The levo-propoxyphene isomer possesses antitussive activity (Miller et al 1963), but negligible analgesic activity. Levo-propoxyphene products were approved and marketed in the US, but have since been discontinued.

Pharmacological studies were conducted in the 1950s and 1960s by administering alpha dextropropoxyphene (hereafter referred to as propoxyphene) to various animal species and comparing the pharmacologic and physiologic responses to the effects obtained from known drugs. In animals and/or humans, effects included analgesia, euphoria, respiratory depression, and gastrointestinal stasis effects. Nonlethal toxicologic signs at high doses in dogs include ataxia, vocalization, tremors and convulsions (Emmerson et al 1971). The therapeutic pharmacodynamic properties have since been attributed to activation of multiple opioid receptor subtypes. Its analgesic effects were considered "weak" at the time of development, but this was considered advantageous since it lacked "strong" morphine-like addictive properties (based on human use), although it has been and still is classified with narcotics.

Two salt formulations of propoxyphene were developed, initially the hydrochloride salt, followed by the napsylate salt of propoxyphene. With oral administration, the napsylate salt is absorbed more slowly than that of the hydrochloride salt since it has a lower

solubility; however, oral bioavailabilities are approximately equal. Excretion occurs through renal (with less than 10% as the parent compound propoxyphene) and biliary routes. Propoxyphene has a circulatory half-life of 6 to 12 hours in the human (Flanagan et al., 1985).

Norpropoxyphene

The toxicity, particularly cardiotoxicity, of propoxyphene is often attributed to the major metabolite norpropoxyphene (Appendix Figure 2; Nickander et al., 1984). CYP3A4 is the main metabolic enzyme in involved in norpropoxyphene formation. Early work suggested that propoxyphene metabolism was due to CYP2D6 based on evidence it was a substrate and inhibitor of CYP2D6 (Sanz and Bertilsson 1990; Kerry *et al.* 1994). However, recent evidence with human subjects that are known fast or slow CYP2D6 metabolizers indicated no alteration of propoxyphene metabolism, and this was confirmed with in vitro metabolism studies with liver microsomes obtained from these genotyped subjects (Somogyi et al., 2004).

Compared to propoxyphene, norpropoxyphene lacks significant opioid activity, has less CNS depressant activity, and has a slightly greater local anesthetic effect (Nickander et al., 1977, 1984). Norpropoxyphene has a half-life of 30-36 hours in man (Flanagan et al., 1985), much longer than propoxyphene. Norpropoxyphene is excreted through renal and biliary routes similar to the parent compound (Nickander et al., 1984).

Based on pharmacology and toxicokinetics, it has been proposed that the accumulation of norpropoxyphene likely contributes to and may precipitate CNS depression, cardiac arrest and respiratory depression and death (Bennet 1993; Davis et al 1996).

Receptor Interactions

Opiate Receptors

Opiate receptor studies were conducted by Lochner and Hynes (1984; refer to Appendix Figure 3). Using [^{3}H]-naloxone as a mu receptor ligand, propoxyphene had a K_i of 492 nM which is comparable to codeine (K_i = 600 nM). This affinity for the mu-opiate receptor was substantially less than morphine (K_i = 6 nM), and l-methadone (K_i =10 nM). For delta opioid activity, propoxyphene had a K_i of 367 nM, approximately equal to that of its mu opioid receptor affinity. It essentially had no activity at kappa opiate receptors. Of importance, norpropoxyphene lacked activity at these opiate receptor subtypes. Although interactions with mu1, mu2 and kappa opiate receptors have been invoked to explain the behavioral and physiological responses in animals and humans, supporting data for these claims has not been identified from the published literature.

In recent years propoxyphene interaction with other types of receptors and with ion channels indicates that propoxyphene is not solely a opiate receptor ligand, a conclusion suggested by Nickander in 1977 upon review of propoxyphene pharmacology. These include activity as:

- Na channel antagonist
- K+ channel modulator (involved in cardiac cell repolarization)
- Nicotinic receptor ($\alpha 3\beta 4$) antagonist (noncompetitive)
- N-methyl-D-aspartate (NMDA) receptor antagonist (noncompetitive)

Besides the possible contributions to analgesia, several of these non-opioid receptor interactions likely contribute to cardiotoxicity and are discussed below.

Na^+ Channel

Propoxyphene and norpropoxyphene possesses a local anesthetic effect similar to that of lidocaine evidenced by a reduction in action potential amplitude after electrical stimulation of cervical sympathetic nerve preparations in vitro (Nickander 1977; refer to Appendix Figure 4). The metabolite, norpropoxyphene, is slightly more potent than dextropropoxyphene, and both are approximately an order of magnitude more potent than lidocaine. Both propoxyphene and norpropoxyphene thus appear to have qualities that are characteristics of Class IC anti-arrhythmics. Lidocaine was an effective treatment for a patient with propoxyphene overdose and exhibiting QRS widening (Whitcomb et al 1989). Further study of this effect conducted with in vitro cultures of rabbit heart atrial cells demonstrated that both lidocaine and propoxyphene blocked inward sodium current, in agreement with the findings described by Nickander (1977). Further analysis of the binding kinetics of propoxyphene and lidocaine provided evidence that the rapid binding-dissociation kinetics of lidocaine to the Na^+ channel displaced propoxyphene which possesses slower dissociation kinetics. Norpropoxyphene concentrations were not determined in the patient and similar in vitro studies with norpropoxyphene were not conducted by Whitcomb and colleagues (1989).

K^+ Channel (hERG channels)

Repolarization of action potentials in cardiac muscle involves a rapidly-activating delayed rectifier K^+ current that are commonly evaluated in studies using Xenopus oocytes transfected with human ether-a-go-go-related gene (hERG) K^+ channels. Using this model, Ulens and colleagues (1999) found that low concentrations (5 μmol/L) of propoxyphene and norpropoxyphene facilitated hERG currents, while higher drug concentrations blocked hERG currents (IC_{50} ~40 μmol/L). Both compounds also slowed K^+ channel activation deactivation kinetics. Therefore both propoxyphene and norpropoxyphene have the potential to alter gating properties of cardiac muscle. They also found a reversal potential shift to a more positive value because of a 30-fold increase in Na^+-permeability, however whether this alteration in Na^+-permeability is confined to the oocyte preparation or can be extrapolated to mammalian cardiac cells remains unclear.

Nicotinic Receptor

In recent years there has been a renewed interest in the analgesic potential of drugs that act at nicotinic receptors. Xiao and colleagues (2001) studied the effects of methadone and related analgesics that included propoxyphene on rat α3β4 neuronal acetylcholine (nicotinic) receptors stably expressed in a human embryonic kidney (HEK 293) cell line. They demonstrated that methadone and its metabolite, as well as propoxyphene, are potent noncompetitive nicotinic receptor antagonists (inhibited nicotine-stimulated rubidium [$^{86}Rb^{+}$] efflux from $^{86}Rb^{+}$ preloaded cells in a concentration-dependent manner with an IC_{50} value for methadone 1.9 ± 0.2 μM, propoxyphene 2.7 ± 0.4 μM, and norpropoxyphene 1.8 ± 0.1 μM). The maximum nicotine-stimulated $^{86}Rb^{+}$ efflux was markedly decreased, but the EC_{50} value for nicotine stimulation was minimally altered indicating a noncompetitive block of the α3β4 nicotinic receptor. This finding is also consistent with the observation that neither methadone, its metabolites, nor its structural analogs competed effectively with [^{3}H]-epibatidine for the agonist recognition site of the neuronal acetylcholine receptor

N-methyl-D-aspartate (NMDA) Receptor

Ebert and colleagues 1998a evaluated opiate drugs for their potential to affect the phenomenon of "wind-up" in neuropathic pain in which hyperalgesia develops following a series of constant repetitive stimuli and is highly dependent on NMDA receptor activation. In this receptor binding study, they demonstrated that propoxyphene has a high affinity (IC_{50} = 5 μM) as an antagonist at rat brain cortex NMDA receptors using the ^{3}H-MK-801 ligand. Further study indicated the binding to be noncompetitive. This is similar to methadone (Gorman et al 1997), but other opiate analgesics such as codeine, etorphine, fentanyl or morphine lacked direct NMDA receptor activity (Ebert et al. 1998a, 1998b).

Cardiotoxicity

Studies Submitted to the FDA

Eli Lilly submitted a number of nonclinical studies in their applications for the development and approval of various propoxyphene formulations from the 1950s to the 1970s. These applications incorporated various evaluations of cardiovascular toxicity, the results of which have been published in the medical literature and incorporated into a number of reviews (Nickander et al 1977, 1984; Barkin 2006).

In 1980, the FDA reevaluated clinical and nonclinical dextropropoxyphene toxicity in response to issues raised in a Nov 21, 1978 Petition to the FDA by the Health Research Group of Public Citizen and that subsequently was discussed at an Advisory Committee meeting in 1979. Lilly also provided published in vitro studies of utilizing cardiac tissue of cats (Amsterdam et al., 1981) and dogs (Holland and Steinberg, 1979), in vivo cardiovascular studies in conscious rabbits (Lund-Jacobsen et al 1978), and in vivo ECG

studies of dogs (Holland and Steinberg, 1979; Page et al 1979). These are summarized in Appendix Figures 5 and 6; from Nickander 1984)

Dose-dependent negative inotropic effects of propoxyphene and norpropoxyphene on isolated rabbit cardiac papillary muscle were demonstrated by Amsterdam and colleagues (1981). In combination, an additive effect was demonstrated. The negative inotropic effects were not reversed with naloxone, but was reversed with isoproterenol. As previously indicated altered conduction through Na^+ channels and nicotinic receptors may be mechanisms for this observation. Thus, either of these compounds could be detrimental to cardiac function at concentrations greater than therapeutic levels.

In 1983 additional studies were submitted evaluating cardiovascular function, ECG and plasma concentrations of propoxyphene and norpropoxyphene. In the dog after a single 50 mg/kg dose of propoxyphene napsylate, peak propoxyphene and norpropoxyphene concentrations were 2.3 µg/mL and 18.4 µg/mL, respectively (Page et al., 1979), which is generally considered above the lethal limits in man.

In a pig model of circulatory shock, Sorenson and colleagues (1984, 1985; a preliminary manuscript was submitted to the FDA by Eli Lilly in 1983 that conveyed a more quantitative analysis of the results) administered propoxyphene intravenously at 15 mg/min to pentobarbital anesthetized pigs until the animals were in cardiovascular shock defined as systolic blood pressure below 60 mm Hg and a cardiac index of approximately 2.0 L/min/m^2. This resulted in a total administered dose of 675 to 2025 mg of propoxyphene corresponding to plasma concentrations of propoxyphene and norpropoxyphene concentrations ranging from 9.6 to 15.3 µg/mL and 0.7 to 2.0 µg/mL. It is not clear if the lower norpropoxyphene levels in pigs are due to differences in metabolism, compared to values found in other species; however, the intravenous route of administration coupled with metabolic competition for CYP3A4 by pentobarbital may be the explanation. Nevertheless, these data indicate that elevated propoxyphene concentrations, in the presence of relatively lower norpropoxyphene concentrations than the dog or human, has detrimental effects on cardiovascular function in the pig model. The effects noted during propoxyphene infusion included respiratory hypoxia with subsequent peripheral vasodilatation, reduction of arterial pressure, left ventricular contractility, and cardiac output. Prolongation of the PQ and QRS intervals occurred but sinus rhythm was maintained until just before death. The absence of a compensatory tachycardia in the face of hypotension and circulatory collapse might be indicative of an indirect CNS depression or a direct effect on cardiac (i.e. baroreceptor) reflexes or nerve conduction.

Eli Lilly also conducted a conscious dog ECG study to address issues concerning polysubstance abuse and the potential for synergistic cardiotoxicity. In this study, which was submitted to the FDA in 1983, propoxyphene was administered together with ethanol and diazepam. Propoxyphene administration alone resulted in increases in the QRS (6-8%), and QTc interval (7-12%). Alcohol, but not diazepam increased the PR interval (8-18%), but there were no additional effects on QRS, or QT intervals. Following a single 50 mg/mL dose of propoxyphene peak plasma propoxyphene and norpropoxyphene

concentrations were 0.52 μg/mL and 1.60 μg/mL, respectively. With twice daily dosing for 4 to 7 days, the peak plasma propoxyphene concentrations remained fairly level at 0.47 to 0.68 μg/mL, but norpropoxyphene concentrations increased to 3.35 to 4.17 μg/mL.

Other than the aforementioned articles and relevant studies by the Applicant, no additional nonclinical toxicology studies regarding propoxyphene and the active metabolite norpropoxyphene have been submitted to the FDA or published in the scientific literature

Conclusions

Propoxyphene was characterized as a "weak" opiate analgesic, advantageous for analgesia at the time of approval, since less narcotic dependency and abuse would be expected. In nonclinical studies submitted for NDA approval in the 1950's and 1960's, there were no animal deaths that could be attributed to cardiovascular changes. Histopathic evaluation of the heart was unremarkable. Deaths at high doses were preceded by CNS signs, ataxia, tremors and convulsions, although again in hindsight, cardiovascular events may have preceded or contributed to these events. Nonclinical studies conducted in response to the 1979 Advisory Committee meeting revealed small dose-related changes in prolongation of PR, QRS, and QTc intervals in association with reduced cardiac function. Recent receptor studies provide evidence that propoxyphene and/or norpropoxyphene may directly influence cardiac function through Na^+ channels and K^+ repolarization (hERG) channels of cardiac myocytes, or through interaction at neural α3β4 nicotinic receptors and NMDA receptors.

Thus the nonclinical studies support the clinical findings and the hypothesis that deaths due to overdose of propoxyphene could be due to cardiotoxicity from propoxyphene and/or norpropoxyphene. Unfortunately, whether these effects occur at therapeutic dose levels is uncertain from the in vivo animal studies submitted to the various propoxyphene NDAs, since there is insufficient animal toxicokinetic information with which to compare to human exposure.

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Figure 1
Structures of propoxyphene, norpropoxyphene, and methadone

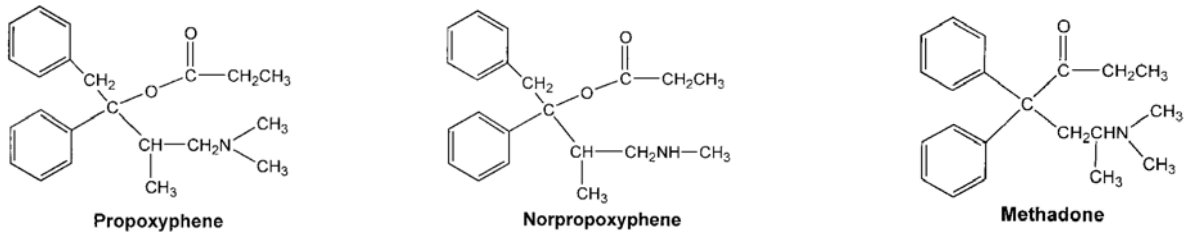

Figure 2
Propoxyphene Metabolism (from Nickander et al., 1984)

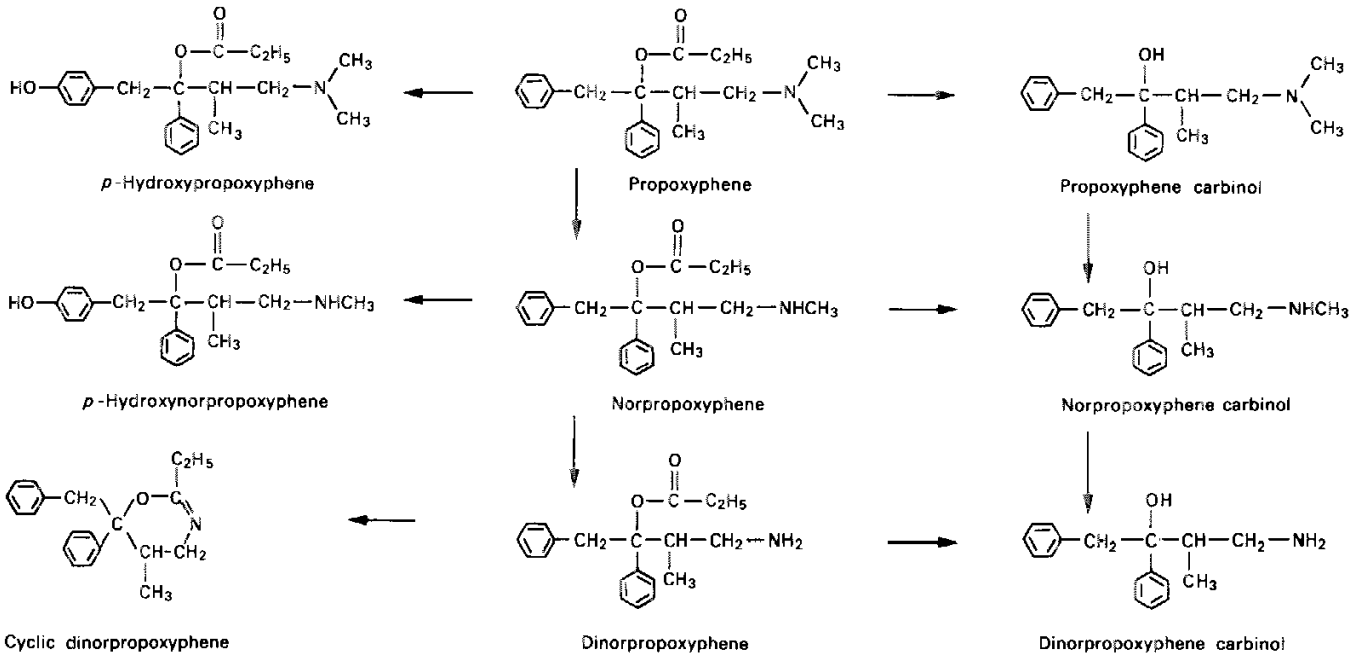

Figure 2 Pathways of biotransformation of dextropropoxyphene in man and animals

Figure 3
Opiate Receptor Binding (Lochner and Hynes 1984)

Table 1 Affinity of dextropropoxyphene for opioid receptors labelled *in vitro* with [^{3}H]naloxone, [^{3}H]-D-Ala^2-D-Leu^5-enkephalin or [^{3}H]ethylketocyclazocine with reference to standard analgesics

	Inhibition of stereospecific binding K_I *(nM)*		
Compound	*[^{3}H]Naloxone (μ site)*	*[^{3}H]-D-Ala^2-D-Leu^5-Enkephalin (δ site)*	*[^{3}H]Ethylketocyclazocine (κ site)*
Buprenorphine	1	10	17
Butorphanol	2	5	2
Morphine	6	74	167
Pentazocine	7	50	75
Nalbuphine	10	59	28
l-Methadone	10	63	>1000
Met-Enkephalin	39	6	>1000
Dextropropoxyphene	492	367	>1000
Codeine	600	5600	>1000
d,l-Propoxyphene hydrochloride	>1000	>1000	>1000
d-Propoxyphene napsylate	527	412	>1000
d-Propoxyphene hydrochloride	492	367	>1000
l-Propoxyphene napsylate	>1000	>1000	>1000
d-Norpropoxyphene	>1000	>1000	>1000
d,l-Dinorpropoxyphene	>1000	>1000	>1000

Figure 4
Local Anesthetic-like Effect (Nickander 1977)

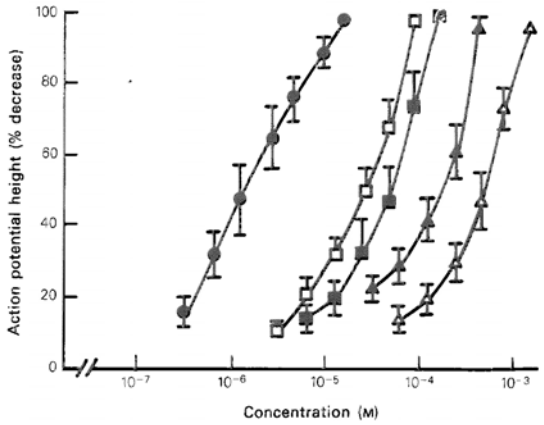

Figure 5 Inhibition of cervical sympathetic action potential amplitude by dextropropoxyphene, norpropoxyphene and local anaesthetics. Ordinate; action potential height expressed as percentage decrease from control amplitude: dibucaine (●), norpropoxyphene (□); dextropropoxyphene (■); cocaine (▲); lidocaine (△). Each point represents the percentage decrease (mean ± SE) in four to seven tissues. (Reproduced by permission, Nickander *et al.*, 1977)

Figure 5
Summary of cardiac effects in isolated tissues (from Nickander 1984)

Table 6 Cardiac effects of dextropropoxyphene or norpropoxyphene in isolated tissues

	Effect	*Concentration P/NP (μg/ml)*	*Reference*
Canine Purkinje fibre action potential			
Duration	↓+++	1/1	Holland & Steinberg (1979)
Rate of rise	↓++	3/1	
Contractility			
Papillary muscle	↓+	3/1	Amsterdam *et al.* (1981)
Atria	↓+	10/3	Holland & Steinberg (1979)
Atrial rate	↓+	3/3	Holland & Steinberg (1979)

P or NP refers to minimum concentration of dextropropoxyphene or norpropoxyphene added to tissue bath causing indicated effect

Figure 6
Summary of cardiac effects in intact animals (from Nickander 1984)

Table 7 Acute cardiovascular effects of dextropropoxyphene or norpropoxyphene in intact animals

	Effect	*Blood concentration P/NP (μg/ml)*	*Reference*
PR interval (AH interval)	↑+++	1.5/2	Holland & Steinberg (1979) Lund-Jacobsen (1978)
QRS duration (HV interval)	↑++	2/1.5	Holland & Steinberg (1979) Lund-Jacobsen (1978)
Heart rate	↓+	3/—	Holland & Steinberg (1979) Lund-Jacobsen (1978) Sorenson (1984)
Contractility (dP/dt)	↓++	3/—	Sorenson (1984)
Mean blood pressure	↓++	5/—	Sorenson (1984)

P or NP refers to minimum level of dextropropoxyphene or norpropoxyphene respectively, causing the indicated effect. NP levels reflect dosing with that substance rather than that formed from P

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-10997	ORIG-1	XANODYNE PHARMACEUTICS INC	DARVON (PROPOXYPHENE HYDROCHLROIDE) CAPS

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/s/

LAWRENCE S LESHIN
01/26/2010

ADAM M WASSERMAN
01/26/2010
I concur with Dr. Leshin's evaluation.