EVIDENCE ON THE CARCINOGENICITY OF

VERAPAMIL

FINAL

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Reproductive and Cancer Hazard Assessment Section
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PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq*.) requires that the Governor cause to be published a list of those chemicals "known to the state" to cause cancer or reproductive toxicity. The Act specifies that "a chemical is known to the state to cause cancer or reproductive toxicity…if in the opinion of the state's qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity." The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. The "state's qualified experts" regarding findings of carcinogenicity are identified as the members of the Carcinogen Identification Committee of the OEHHA Science Advisory Board (per Title 22 California Code of Regulations, section 12301) (referred to hereafter as the Committee).

Verapamil was assigned a final priority of 'high' carcinogenicity concern and placed on the Final Candidate list of chemicals for Committee review on March 12, 2004. A public request for information relevant to the assessment on the evidence on the carcinogenicity of this chemical was announced in the *California Regulatory Notice Register* on March 12, 2004. No information was received as a result of this request. This document was developed to provide the Committee with the available scientific evidence on the carcinogenic potential of verapamil. It was released as a draft document in August 2004. No public comments were received on the draft document.

At their November 1, 2004 meeting the Committee, by a vote of none in favor and five against, did not find that verapamil had been "clearly shown through scientifically valid testing according to generally accepted principles to cause cancer." Accordingly, verapamil was not placed on the Proposition 65 list of chemicals known to the State to cause cancer.

The following is the final version of the document that was discussed by the Committee at their November 2004 meeting.

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1 EXECUTIVE SUMMARY

Verapamil, administered as its hydrochloride, is a calcium channel blocker used for the treatment of angina, arrhythmia, and essential hypertension. Millions of people throughout the world are currently taking calcium channel blockers including verapamil to treat hypertension and other cardiovascular problems. The current number of prescriptions in California was not available.

Twelve epidemiologic studies of human use of verapamil studies were identified, including eight cohort and four case-control studies. Although not all studies found a significantly increased risk, overall cancer risk was consistently higher in verapamil-exposed subjects in these studies, with an approximate doubling of risk in the studies that best controlled for potential confounding. Only a few studies provided results for specific cancer sites. A well-designed cohort study found an increased risk of lymphatic and hematopoietic cancer associated with verapamil exposure, and a well-designed case-control study found an increased risk of breast cancer. A more limited case-control study found an indication of increased colon cancer risk with verapamil exposure, and a limited cohort study found an increased risk of respiratory cancer in women. These findings are consistent with results in some but not all studies which examined site-specific results only for subjects exposed to any CCB (including verapamil). In the best, most recently conducted cohort study, evidence of a dose-response effect with verapamil exposure was seen for overall cancer risk and exposure duration (as a measure of cumulative exposure) as well as for overall cancer risk and daily dose level. The case-control study of breast cancer also provided an indication of an effect of dose in terms of duration of exposure. Further studies are needed to refine the risk estimates for these effects, and to examine the impact of age, gender, and dosing (including drug formulation) on cancer risk.

No animal carcinogenicity studies of verapamil have been reported in the published scientific literature. Two sets of studies in rats – one consisting of administration of verapamil in the diet for two years at doses of 1, 3.5 or 12 times the maximum recommended human daily dose, and the other consisting of administration by an unspecified route of verapamil for 18 months at six times the maximum recommended human daily dose – are briefly summarized in labeling language approved by the U.S. Food and Drug Administration for verapamil hydrochloride as providing no evidence of a carcinogenic potential.

With regard to potential genotoxicity, one set of studies with human lymphocytes has shown clastogenic effects both *in vitro* and *in vivo*, although studies with other species have not shown such effects. There has been only limited testing of verapamil in standard tests of mutagenicity. Verapamil alone is not mutagenic in *Salmonella* assays. Verapamil has been shown to enhance the effects of certain genotoxic agents in both bacteria and in mammalian cells. On the other hand, in several studies in animals, co-administration of verapamil with known carcinogens has had the effect of reducing tumor incidence.

The mechanism by which verapamil may induce tumors is unknown. While various hypotheses have been suggested (e.g., inhibition of apoptosis; intracellular accumulation of genotoxic agents; direct genotoxicity), there is not a robust dataset supporting any of the hypotheses.

Further, the data that do exist provide conflicting results with respect to verapamil's genotoxicity and its ability to suppress apoptosis.

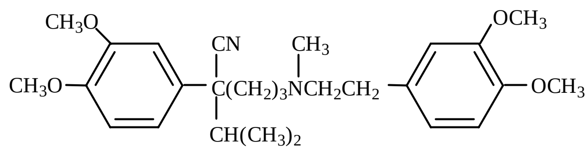
With respect to pharmacokinetics and metabolism of verapamil, factors which might increase internal exposure to verapamil and/or specific verapamil metabolites include age, gender, genetic predisposition, and concomitant xenobiotic exposures. Bioavailability is increased in older (> 60 years) individuals, presumably because of decreased first-pass metabolism. Bioavailablity was somewhat higher in women; the elimination half-life was longer in women compared to men for both oral and intravenous administration. Information on tissue distribution shortly after verapamil administration from studies in humans, dogs and rats found the highest concentrations in the lung for all three species. Studies in rats indicate that the elimination rate varies across tissues, with elimination in the lungs and kidney occurring only half as rapidly as in the brain, heart and liver.

In conclusion, findings in epidemiologic studies of subjects taking verapamil on the whole indicate an increased risk of cancer, with an approximate doubling of overall cancer risk in the two cohort and one case-control studies that best controlled for potential confounding, and indications of a dose-response for both duration of use and daily verapamil intake in the best study conducted to date. Significant findings for specific cancer sites include increased risks of lymphatic and hematopoietic cancer in the best-designed cohort study, as well as significant findings from case-control studies of breast and colon cancer; results in some but not all studies which examined site-specific results only for subjects exposed to any CCB (including verapamil) were elevated for these same sites. The mechanism by which verapamil may cause cancer is unknown. Studies of pharmacokinetics and metabolism suggest that specific factors which might increase internal exposure to verapamil and/or specific verapamil metabolites include older age, gender (i.e., being female), and concomitant xenobiotic exposures.

2 INTRODUCTION

2.1 Identity of Verapamil and Verapamil Hydrochloride

Figure 1. Structure of verapamil

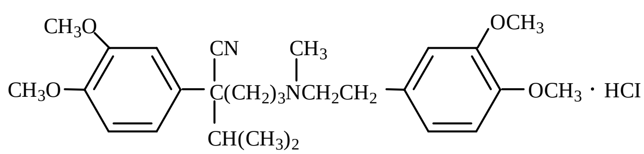


$C_{27}H_{38}N_2O_4$ M.W. = 454 · 6

Molecular Formula: $C_{27}H_{38}N_2O_4$
Molecular Weight: 454.6
CAS Registry No. 52-53-9
Chemical Class: Diphenylalkylamine; Calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist).

Synonyms: Benzeneacetonitrile, alpha-[3-[[2-(3,4,-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-alpha-(1-methlethyl).

Figure 2. Structure of verapamil hydrochloride.



$C_{27}H_{38}N_2O_4$. HCI M.W. = 491· 08

Molecular Formula: $C_{27}H_{38}N_2O_4 \bullet HCl$
Molecular Weight: 491.08
CAS Registry No. 152-11-4
Chemical Class: Diphenylalkylamine; Calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist).

Synonyms: Benzeneacetonitrile, alpha-[3-[[2-(3,4,-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-alpha-(1-methlethyl) hydrochloride; Calan®; Calan SR®; Covera-HS®; Isoptin® SR; Verelan® PM.

2.2 Occurrence and Use

Verapamil is manufactured for use in pharmaceutical formulations as verapamil hydrochloride. Verapamil hydrochloride is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) marketed under various trade names, including Calan®, Covera-HS®, Isoptin® SR and Verelan® PM for the treatment of angina, arrhythmia, and essential hypertension. The usual initial dose is 180 mg of verapamil hydrochloride, with lower doses of 120 mg a day suggested for patients who have an increased response to verapamil (e.g., the elderly or people of smaller physical stature). Doses of up to 240 mg every 12 hours (480 mg/day) may be given, depending on therapeutic efficacy and safety (Physician's Desk Reference, 2004). Different formulations have been developed, which vary the manner in which verapamil is released (e.g., "immediate release", "sustained release"). Millions of patients are currently taking calcium antagonists including verapamil to treat hypertension and other cardiovascular problems (Pahor and Furberg, 1998).

The results of a recently conducted, large clinical trial (n=16,602 patients in 15 countries) conducted by Black *et al.* (2003) on the efficacy of controlled-onset extended release (COER) verapamil in treating the conditions for which it is prescribed found that COER verapamil "did not demonstrate equivalence…compared with a regimen beginning with a diuretic or beta-blocker." For most cardiovascular outcomes studied, such as stroke or any cardiovascular death, treatment with verapamil was not associated with reduced risk level compared to the control group (patients being treated with other anti-hypertensive drugs). One outcome, non-stroke hemorrhage, was significantly increased in participants in the COER-verapamil group compared with controls. The effect these results may have on prescribing practices is unknown.

3 DATA ON CARCINOGENICITY OF VERAPAMIL AND VERAPAMIL HYDROCHLORIDE

Twelve epidemiologic studies of cancer incidence in patients taking verapamil for cardiovascular problems have been conducted. The carcinogenicity of verapamil has also been studied in male and female rats exposed via diet for two years and in rats exposed via an unspecified route for 18 months. Verapamil has been tested in a variety of *in vivo* and *in vitro* short-term tests including clastogenicity assays in mice and humans, *Salmonella* reverse mutation assays, and assays for genotoxicity in human lymphocytes and hamster cells. These same test systems have also been employed to investigate verapamil's potential to influence the genotoxicity of other compounds. Several studies in rats and mice have examined the effects of verapamil treatment on the tumorigenicity of other known carcinogens. Endpoints related to cell proliferation have been examined in various *in vivo* and *in vitro* mammalian test systems. The metabolism and pharmacokinetics of verapamil have also been extensively studied.

3.1 Carcinogenicity Studies in Humans

A body of data has been developing over the past eight years regarding the potential for calcium channel blockers (CCBs) to increase the risk of cancer in human populations. Use of CCBs in treatment of hypertension and coronary artery disease began in the 1980s, and gained popularity in the early 1990s. Thus, a relatively short time period has elapsed since large numbers of individuals initiated treatment with these drugs. The earliest study to raise a concern about cancer risk, conducted in the mid-1990s (Pahor *et al.*, 1996a and 1996b), found significantly elevated risks of overall cancer for any CCB use and for two specific drugs, verapamil and nifedipine. Since then, other investigators have sought to replicate or refute these associations, often by studying cohorts that had been previously assembled to investigate cardiovascular diseases.

The group of pharmaceutical agents considered to be calcium channel blockers, sometimes called calcium antagonists, includes different chemical classes: dihydropyridines (e.g., nifedipine, felodipine, and amlodipine), diphenylakylamines (e.g., verapamil, fendiline), and benzothiazepines (e.g., diltiazem). Many studies of cancer risk in patients using CCBs have grouped together all of the drugs with calcium channel blocking activity. The choice to examine the effect of these different drugs as a group appears to be based on an assumption that CCBs might promote cancer through a common underlying biological process, such as interference with apoptosis. Blocking calcium may interfere with apoptosis, a type of programmed cell death and one mechanism through which cancer growth can be checked. A rise in cytosolic calcium is one of the known triggers for apoptosis in some cells. This mechanism would have the potential to affect many cancer sites, rather than a particular one.

Some studies have examined use of specific classes of CCB, and the effect seen across classes has been far from uniform. In particular, overall cancer risks associated with use of verapamil have been consistently higher than the risks seen in the same study for any CCB use or for use of other specific CCBs. However, some of the same cancer sites have been elevated in studies that considered verapamil-exposed subjects separately and in other studies that looked at all CCB-exposed (including verapamil-exposed) subjects together. Below we summarize the available studies, and present verapamil-specific cancer risk estimates, including site-specific risk estimates where available (Tables 1 - 7). For comparison purposes, site-specific cancer risk estimates from these studies in relation to use of any CCB are also summarized (Tables 8 and 9). Study findings and limitations are then discussed with respect to verapamil's potential carcinogenicity.

Study summaries

Twelve studies were identified which provided results for verapamil-exposed subjects, including eight cohort and four case-control studies. Cohort studies with verapamil-specific results for overall or site-specific cancers are summarized in the following order. First, two studies (Tables 1 and 2) are described, both of which compared risks within cohorts of elderly persons (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al.*, 2003) and controlled for hypertension and other factors of concern. Pahor *et al.* (1996a and 1996b) were the first to observe an increased risk with CCB exposure. Beiderbeck-Noll *et al.* (2003) replicated the analyses of this initial investigation in a different cohort, as well as providing more extensive analyses. Second, studies which compared risks within cohorts of elderly (Fitzpatrick *et al.*, 1997; Cohen *et al.*, 2000) or other persons (Braun *et al.*, 1998), with some control for factors of concern but with serious limitations due to numbers of subjects (Fitzpatrick *et al.*, 1997; Cohen *et al.*, 2000) or length of observation time (Braun *et al.*, 1998) are summarized (Table 3). Finally, two studies which compared cancer rates of verapamil users with those of the general population are summarized (Olsen *et al.*, 1997a; Sajadieh *et al.*, 1999) (Table 4), as is a third study (Hole *et al.*, 1998) which used cancer rates in a separate large cohort of persons from a nearby area for comparisons of verapamil users while other comparisons used general population rates (Table 5). The last three studies adjusted for age and gender, but did not otherwise address factors of concern. They also suffered from short observation time (Olsen *et al.*, 1997a) or incomplete exposure information (Hole *et al.*, 1998; Sajadieh *et al.*, 1999), severely limiting their ability to detect an effect. Of the four case-control studies of verapamil exposure available, two considered overall cancer risk (Table 6), with one (Jick *et al.*, 1997) comparing risks between groups of hypertensive subjects, and the other (Rosenberg *et al.*, 1998) using hospital-based subject selection. The other two case-control studies explored single cancer sites (Table 7), one as a hypothesis-generating exploration of colon cancer (Hardell *et al.*, 1996), and the other as a focused investigation of breast cancer with reasonably good control for confounders (Meier *et al.*, 2000).

Cohort studies

Pahor et al. (1996a; 1996b)

Pahor *et al.* (1996a; 1996b) examined incidence of cancer in a prospective cohort study of predominantly white (94%) and female (64%) persons aged 71 years or more from three regions of the U.S. (the Established Populations for Epidemiologic Studies of the Elderly, EPESE) (Table 1). In one report, those taking calcium channel blockers (n=451) were compared with all other participants (n=4601) (Pahor *et al.*, 1996a). A separately published analysis (Pahor *et al.*, 1996b), limited to those with hypertension with single-drug antihypertensive treatment (n=750), examined cancer risk among this population in relation to the medications used to treat hypertension; those using calcium channel blockers (n=202) were compared with persons using beta blockers (n=424). In both analyses, relative risks were adjusted for age, gender, race, smoking, body mass index, and number of hospital admissions not related to cancer. Drug use data were collected by container label examinations and interviews in 1988 that asked about verapamil use during the previous two weeks. Maximum time since first documented exposure was five years. Despite the fact that the cohort had been followed since 1982-83, no data on prior exposure were used in the analyses. Data on exposure subsequent to the interview were also lacking.

In the cohort as a whole, verapamil use (n=118) was associated with a statistically significant elevated overall cancer risk (RR=2.49, 95% CI=1.54-4.01) (Pahor *et al.*, 1996a). In the analysis limited to hypertensives (n=65), the relative risk was nearly identical, with slightly larger confidence limits (RR=2.46, 95% CI=1.17-5.17) (Pahor *et al.*, 1996b). Study participants taking verapamil had the highest rates of cancer, while risks among those using the other calcium channel blockers in the study were also elevated in both analyses (nifedipine, RR=1.74, 95% CI=1.05-2.88; diltiazem, RR=1.22, 95% CI=0.70-2.12; these values reflect the full cohort analysis, Pahor *et al.*, 1996a). Analyses of verapamil (and other specific CCBs) were limited to those taking only one CCB.

Any calcium channel blocker usage (including verapamil) conferred a statistically significant increased cancer risk in both analyses (Pahor *et al.*, 1996a; 1996b). The study of hypertensives found a doubling of risk for all cancers with CCB use (RR=2.02, 95% CI=1.16-3.54) (Pahor *et al.*, 1996b); cancer risk with CCB use in the larger cohort was also elevated but slightly lower (RR=1.72, 95% CI=1.27-2.34) (Pahor *et al.*, 1996a). Specific cancer sites with elevated risks (Table 8) included: stomach; colon; rectum; breast; uterus; prostate; a grouping of bladder, ureter and kidney; and lymphatic and hematopoietic cancers (LHC), with uterus and LHC being statistically significant.

Pahor *et al.* (1996b), the first of the two analyses to be published, drew many letters (Leader and Mallick, 1996; Mason, 1996; Moslen and Balakumaran, 1996; Zimlichman, 1996; Brandenburg *et al.*, 1996; Trentwalder, 1997) raising important considerations regarding the study. These included the lack of precise information about drug exposure; selectivity in examining the subset of hypertensives chosen from the full cohort, including the resulting reduction in study size; and choice of those who used beta-blockers as the comparison group, the hypothesized mechanism by which an effect such as that found in this study could be occurring, and the conclusions which could be drawn from the study. The authors, both in response to specific comments (Pahor *et al.*, 1996c) and by publication of the analyses of the full cohort (Pahor *et al.*, 1996a) acknowledged the issues and encouraged others to more fully address them in subsequent research. The depth of interest in the topic has been reflected in the many studies which have been conducted in subsequent years, through which most if not all of the concerns raised have been addressed. The study by Beiderbeck-Noll *et al.* (2003) in particular was designed to replicate the Pahor *et al.* analyses and go beyond them.

Beiderbeck-Noll et al., 2003

Beiderbeck-Noll *et al.* (2003) reported on a prospective, population-based cohort study of 3204 subjects 71 years of age or older who were followed for up to eight years (mean, 5.2 years) in Rotterdam, the Netherlands (Table 2). More subjects were women (>65%) and most were nonsmokers (>80%), although many (38.9% of CCB users) had formerly smoked; information on race was not reported. CCB exposure was determined through baseline interviews (1990-93) which collected information from subjects on currently used prescription drugs; these were repeated in second (1994-96) and third interviews (1997-99). Cumulative exposure was evaluated based on automated pharmacy record data. Hospital admission with a diagnosis of malignant cancer (first occurrence) was identified through a nationwide registry. Extensive information on potential confounders was collected.

Because the investigators hoped to examine whether including better-defined potential confounders or more detailed exposure assessment would weaken or eliminate the relationship between CCB use and cancer first reported by Pahor *et al.* (1996a), they used three different models to examine the association. The first (Model 1) followed the methods of Pahor *et al.* (1996a), and assessed the rate of cancer in CCB-using subjects 71 years or older at baseline compared to non-CCB users, adjusting for age, gender, smoking status, number of hospital admissions during follow-up, heart failure and alcohol intake. Model 2 relied on an assessment of all measured potential risk factors, and included in the model all factors univariately associated with cancer ($p<0.10$) which caused more than a five percent change in the point estimate; these included ischemic heart disease, total cholesterol, and diabete mellitus. In addition, Model 2 also adjusted for age, gender, diuretics, ACE inhibitors and beta-blockers. Model 3 included adjustment for the factors used in Model 2, and used information from the pharmacy database to examine cumulative exposure.

In the analysis comparable to Pahor *et al.* (1996a) (Model 1), the overall cancer risks seen with verapamil use, while slightly lower than those found by Pahor *et al.* (1996a), were elevated and statistically significant (Model 1: RR=2.1, 95% CI=1.1-4.0, based on nine exposed cases). Adjustment for additional risk factors (Model 2) lowered the estimated risk slightly, but it remained significantly elevated (Model 2: RR=2.0, 95% CI=1.01-3.9).

Risk increased in a dose-dependent manner with daily dose of verapamil, although no cases were seen in the high dose group (low dose: RR=1.7, 95% CI=0.7-4.2; mid-dose: RR=2.7, 95% CI=1.02-7.4; high dose: no cases; model not specified). Using information from the pharmacy database on duration of use (Model 3), the measure of cumulative exposure also provided an indication of a dose-response effect for verapamil. Overall cancer risks were elevated both for shorter and longer cumulative exposure to verapamil (≤2 years: RR=1.4, 95% CI=0.8-2.5; >2 years: RR=2.4, 95% CI=1.2-4.9), and the latter was statistically significant.

Risk of specific cancers associated with verapamil use was generally higher than that of other CCB use, according to the authors. They reported details only for the statistically significant elevated risk associated with verapamil use, which was for LHC (RR=7.84, 95% CI=1.66-37.0; model not specified).

In users of any CCB, the overall cancer risk estimate was elevated, though not to the extent seen in Pahor *et al.* (1996a), and did not reach statistical significance (Model 1: RR=1.4, 95% CI=0.9-2.0); adjustment for additional risk factors (Model 2) lowered the estimated risk (RR=1.2, 95% CI=0.8-1.8). For any CCB, use for two years or less was not associated with an elevated risk, while use for more than two years led to a slightly elevated risk (≤2 years: RR=1.0, 95% CI=0.7-1.5; >2 years: RR=1.3, 95% CI=0.8-2.0).

In the analyses of specific cancer sites and any CCB use, only skin cancer was significantly elevated and only using Model 1 (RR=2.7, 95% CI=1.03-7.3). Statistically nonsignificant elevated relative risks, based on Model 1 analyses of any CCB use, were found for liver, gallbladder, and pancreas (RR=3.1, 95% CI=0.6-14.9), lung (RR=1.3, 95% CI=0.3-5.5), bladder, ureter and kidney (RR=1.5, 95% CI=0.5-5.1), colon (RR=1.4, 95% CI=0.5-3.8), rectum (RR=2.0, 95% CI=0.5-8.8), and LHC (RR=2.0, 95% CI=0.4-8.9); breast cancer risk was not calculated, and no explanation was provided in the report.

Table 1: Pahor *et al.* cohort study of verapamil use and cancer risk

Study author **Cohort characteristics**	**Exposure and outcome definition**	**Exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Pahor *et al.*, 1996a 5052 persons from U.S., 3 regions. Total exposed to verapamil, n=118. *Cohort* Age: ≥71 y, avg age 79.0. Gender: 35.9% male Comparison: within cohort to 4601 non-CCB users.	**Any use of verapamil** All cancer	18	2.49* (1.54-4.01)	Single CCB therapy only. Drug use data collected by interview and container label examination. Avg cohort member followed 3.7 y (max: 5 y). Model adjusted for age, gender, ethnicity, smoking, alcohol use, heart failure and number of hospital admissions not related to cancer. No adjustment for concurrent use of other hypertensive drugs.
Pahor *et al.*, 1996b Subcohort of above, 750 hypertensives. Total exposed to verapamil, n=65. *Cohort* Age: ≥71 y, avg age 77.8. Gender: 35.2% male Comparison: within subcohort to 424 subjects on beta-blockers only.	**Any use of verapamil** All cancer	10	2.46* (1.17-5.17)	Single drug anti-hypertensive treatment only. Drug use data collected by interview and container label examination. Avg cohort member followed 3.7 y (max: 5 y). Models adjusted for age, gender, ethnicity, smoking, BMI and number of hospital admissions not related to cancer.

* $p \leq 0.05$

Abbreviations: avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; y, year.

Table 2: Beiderbeck-Noll *et al.* cohort study of verapamil use and cancer risk

Study author **Cohort characteristics**	**Exposure and outcome definition**	**Exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Beiderbeck-Noll *et al.*, 2003 3204 persons in Rotterdam, the Netherlands. Total number exposed to verapamil not reported. *Cohort* Age: ≥71y, avg age 79.2. Gender:35.5% male Comparison: within cohort to 273 non-CCB users	**Any use of verapamil** Model 1 All cancer	9	Model 1 2.1 * (1.1-4.0)	Single CCB therapy only. Information on drug dosage from container label examined during interview; cumulative use from pharmacy database. Median exposure duration to CCBs: 2 y. Small number of exposed cases. Maximum follow up 8 y. Model 1 adjusted for: age, gender, heart failure, smoking status, hospital admissions, alcohol intake. Model 2 and Model 3 adjusted for: age, gender, IHD, diabetes, use of diuretics, ACE inhibitors and beta-blockers. In Model 3, CCB use was a time-dependent variable. Model used in calculating risks by dose of verapamil and for site-specific (LHC) risks was not specified in the report.
	Model 2 All cancer	9	Model 2 2.0 * (1.01-3.9)	
	Model 3 **≤2y use of verapamil** All cancer	NA	Model 3 1.4 (0.8-2.5)	
	>2 y use of verapamil All cancer	NA	2.4* (1.2-4.9)	
	By verapamil dose **-Low-dose** All cancer	NA	1.7 (0.7-4.2)	
	-Mid-dose All cancer	NA	2.7* (1.02-7.4)	
	-High-dose All cancer	No cases	--	
	Any verapamil use Lymphohemato-poietic cancer	NA	7.8* (1.7-37.0)	

* p≤0.05

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; IHD, ischemic heart disease; LHC, lymphohematopoietic cancer; NA, not available; y, year.

Fitzpatrick et al., 1997

Fitzpatrick *et al.* (1997) reported breast cancer incidence results from a cohort study of 3198 women ≥ 65 years old, drawing from the Cardiovascular Health Study (CHS), a multi-location observational cohort. This study examined the effect of specific formulations of CCBs, immediate release (IR) compared to sustained release (SR) formulations, not considered in other studies. CCB use was assessed at four different visits over a period of up to five years, with average follow-up time after first documented exposure of 3.9 years for IR CCB users, and 2.7 years for SR CCB users.

Verapamil results from this study have not been included in a table in this document, because only unadjusted rates but not relative risks were provided for specific CCBs. For verapamil, the breast cancer incidence rate was much higher for IR users (n=58) than for SR users (n=172) (IR, 15.7 per 1000 person-years at risk, based on three cases; SR, 4.6 per 1000 p-y, based on two cases; no CCB use, 5.1 per 1000 p-y, based on 2439 cases). No verapamil-specific hazard ratios (HR) were presented, as the number of breast cancer cases using verapamil was quite small. Breast cancer incidence in this study was consistently higher in women using IR formulations (any CCB) compared to those using SR formulations (any CCB), and in discussing this finding, the authors noted the longer follow-up time for the IR users.

For those using any CCB, the breast cancer risks were elevated, with an HR of 2.57 (95% CI=1.47-4.49); this and all other HRs were adjusted for age, race, parity and age at menopause and self-reported diabetes. Comparing CCB users with those using other anti-hypertensive drugs led to a more highly elevated risk (HR=2.91, 95% CI=1.41-6.00). The authors hypothesized that women using both estrogen and CCB simultaneously would be at a higher risk for breast cancer than those using either drug alone, and found the HR for combined use of any type of CCB and estrogen (HR=4.48, 95% CI=1.58-12.75) was elevated above that of any CCB use, and use of IR CCB and estrogen produced an even stronger association (HR=8.48, 95% CI=2.99-24.08).

Cohen et al., 2000

Cohen *et al.* (2000) conducted a prospective cohort study of 3511 persons aged 65 years or older living in North Carolina, who were followed for up to ten years after enrollment (Table 3). Average follow-up was not reported. Two-thirds (65.6%) of subjects were women, and more than half (56.8%) were black. At the time of enrollment in the study (baseline) and three and six years later, subjects were asked about use of prescription medicines in the previous two weeks. Exposure to CCBs was defined as continuous if reported at all three interviews. Average daily dose was calculated based on strength of medication and reported number of times taken the day prior to the interview. Hospitalization or death due to cancer (excluding skin cancer) was analyzed, based on data from the Health Care Financing Administration. The total number of subjects taking CCBs increased over time, as did the proportion of CCB users who were using verapamil; by 1992 (six-year follow-up), 131 subjects were using verapamil. However, the authors do not specify the total number of subjects exposed to verapamil at any time during the course of the study, nor do they indicate the number of cases exposed.

Cancer risk for verapamil use was slightly elevated (HR=1.3, 95% CI=0.8-2.2), but did not reach statistical significance. All analyses were adjusted for use of other CCBs, beta-blockers, or ACE inhibitors and for age, race, gender, smoking, baseline health, education, body mass index (BMI), and alcohol use, and considered CCB use as a time-dependent variable.

Total number of cancers among those taking CCBs at any time during the study was not reported; 16 cancers were reported among those (n=133) who were taking CCBs at baseline. The authors noted that the number of cancers was too small to analyze risk by tumor type. Cancer risk for use of any CCB throughout the study was not elevated (HR=0.9, 95% CI=0.6-1.2), although it was slightly but not significantly elevated among black subjects (HR=1.2, 95% CI=0.8-1.8).

Braun et al., 1998

Braun *et al.* (1998) conducted a study of 11,575 subjects who had been screened for heart disease (for another study), 50 percent of whom (n=5,843) were treated with CCBs (Table 3). Concurrent use of diuretics, beta-blockers and ACE inhibitors occurred in both those who did and did not use CCBs. Exposure was defined based on treatment with a CCB at an initial screening visit during 1990-1992. The mean age of subjects was 59.8 years, and 78% were male. The mean follow-up period for cancer incidence after documented exposure was less than three years (34 months; range, 14-46 months), reducing the ability of this study to detect an association between exposure and cancer.

For verapamil users (n=336), overall cancer incidence was not elevated (RR=1.16, 95% CI=0.56-2.38, eight exposed cases), nor was overall cancer mortality (n=350 verapamil users) (RR=1.22, 95% CI=0.53-2.81, six cases) in analyses pooled over strata of age, gender and smoking status.

For all CCB users, overall cancer incidence was not elevated (RR=1.07, 95% CI=0.83-1.37), and neither was overall cancer mortality (RR=1.03, 0.75-1.41).

Olsen et al., 1997a

Olsen *et al.* (1997a) conducted a study in one Danish county of 17,911 persons who had at least one prescription for CCB in 1991-1993 (Table 4). Cancer occurrence (n=412) during a three year follow-up period (ending in December 1993) was determined using files of the Danish Cancer registry, and cohort rates were compared with county-specific rates. About a third of the cohort (32%) were under age 59. Mean follow-up time after first documented prescription was less than two (1.8) years, and 22% had their first prescription for CCB in the same year as the follow-up ended, reducing the ability of this study to detect an effect.

For those taking verapamil only (n=4879) (no other CCBs concurrently), the standardized incidence ratio (SIR) for all cancer incidence (n=152) was not significantly elevated (SIR=1.09, 95% CI=0.92-1.27). No adjustment was made for smoking, BMI, use of other drugs, or other potential confounders. Site-specific SIRs were not presented for those using verapamil.

Table 3: Other cohort studies comparing cancer risk of verapamil use within cohort

Study author **Cohort characteristics**	**Exposure and outcome definition**	**Exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Cohen *et al.*, 2000 3511 persons in North Carolina. Total exposed to verapamil not reported. *Cohort* Age: ≥65 y, avg age 73.4 y. Gender:34.4% male Comparison: within cohort to non-CCB users (number not reported).	**Any use of verapamil** Hospitalization or death due to cancer (excludes skin cancer)	NA	1.3 (0.8-2.2)	Use of multiple CCBs included. Information on dose collected. Avg follow-up not specified, maximum is 10 y. Models included adjustment for age, gender, smoking, education, alcohol use, BMI, medical history, and considered CCB use as a time-dependent variable. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).
Braun *et al.*, 1998 11,575 persons screened for heart disease study. Total exposed to verapamil, n=336. *Cohort* Age: ≤74 y, avg age. 59.8 y Gender: 78% male Comparison: within cohort to 5543 non-CCB users.	**Any use of verapamil** Cancer incidence Cancer death	 8 6	 1.16 (0.56-2.38) 1.22 (0.53-2.81)	Single CCB therapy only. CCB use determined one time only. Small number of exposed cases. Short follow-up 14-46 months (avg 34 months). Estimates obtained using strata to adjust for age, gender and smoking. No control for other potential confounders. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; y, year.

For those taking any CCB, the only statistically significant elevated ratio was for urinary bladder cancer (SIR=1.5, 95% CI=1.1-2.1), and the authors note that this elevated risk was found in men with exclusive use of diltiazem (SIR=2.1, $p \leq 0.05$) or multiple CCB use (SIR=2.6, $p \leq 0.05$).

In a comment, Pahor (1997) noted the short follow-up in this study and that three factors – exposure time, dose, and type of CCB – are potentially important in assessing the association of CCB use and cancer; he urged that future studies consider CCB dose, class, and formulation. In response, Olsen *et al.* (1997b) noted that both this study and Pahor *et al.*'s lacked information on cumulative doses, and reiterated their conclusion that "the lack of association could reflect the relatively short follow-up after registration in the prescription database."

Sajadieh et al., 1999

Sajadieh *et al.* (1999) reported on an analysis of cancer in a cohort of subjects assembled in 1985-87 for study of the effect of treatment with verapamil on mortality and cardiovascular events (e.g., heart attacks), the Danish Verapamil Infarction Trial (DAVIT) (Table 4). Study subjects were persons less than 76 years old who had suffered a heart attack. Most exposed subjects (80%) were male, two-thirds (67.1%) were under age 65, and a majority smoked (63.4%). Follow-up ended at the end of 1993. The mean duration of verapamil use during the trial was just over one year (15 months). Although time since first exposure was known for study subjects, use of verapamil beyond the clinical trial was not investigated, nor was other CCB use known for the time after the trial. Although the cohort as assembled was prospective, randomized, and placebo-controlled, the analysis of cancer risk relied on comparison of cancer rates of the verapamil-exposed subjects (n=878) with rates in the general Danish population.

Risk of cancer in subjects exposed to verapamil during the DAVIT was not elevated for all cancers (men, SIR=0.8, 95% CI=0.6-1.1; women, SIR=0.9, 95% CI=0.4-1.6). Nor were any of the site-specific cancer risks elevated, with the exception of respiratory cancer in women (SIR=3.9, 95% CI=1.3-9.1, based on five subjects) but not men (SIR=0.8, 95% CI=0.4-1.5, based on 10 subjects). Most of the site-specific analyses had fewer than five subjects per tumor site. None of these analyses adjusted for smoking status, concurrent use of other anti-hypertensive drugs, or other potential confounders, other than age (five-year groups) and gender.

Hole et al., 1998

Hole *et al.* (1998) conducted a retrospective cohort study of 2297 hypertensive subjects who received a first CCB prescription at a Glasgow clinic during 1980-1995 (Table 5). Although hypertensive subjects not treated with a CCB were also studied, most risk comparisons were based on rates derived from a separate longitudinal cohort first surveyed in the 1970s, or general population rates for the region (West Scotland). No information on duration of use or dose was reported, and subjects' average follow-up after a first CCB prescription was five years. Only 24% of the original cohort (n=541) were still taking a CCB at a three-year follow-up visit.

Table 4: Cohort studies comparing cancer risk in cohort using verapamil use with general population rates

Study author Cohort characteristics	Exposure and outcome definition	Exposed cancer cases	Relative Risk estimate (95% CI)	Comments
Olsen *et al.*, 1997a 17,911 CCB users in a county in Denmark. Total exposed to verapamil, n=4879. *Cohort* Age: no limits, avg age not given Gender: 49% male Comparison: general population.	**Any use of verapamil** All cancer	 152	 1.09 (0.92-1.27)	Use of multiple CCBs included. Pharmacy database provided drug use information. Authors noted that 2% of general Danish population >50 y (comparison group) takes CCBs. Very short follow-up (≤3 y; avg 1.8 y). No adjustment for potential confounders other than age and gender. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).
Sajadieh *et al.*, 1999 878 persons who had suffered a heart attack, treated with verapamil, 1985-87 in Denmark. *Cohort* Age: <76 y, avg age: not given. Gender: 80% male Comparison: general population	**Any use of verapamil** All cancer: men All cancer: women Respiratory cancer: men Respiratory cancer: women	 46 11 10 5	 0.8 (0.6-1.1) 0.9 (0.4-1.6) 0.8 (0.4-1.5) 3.9* (1.3-9.1)	Use of multiple CCBs included. Avg duration of treatment during 1985-87, 15 months; no information on use afterwards. Despite presence of a placebo-exposed group, calculations based on Danish Cancer Registry. Most (67%) subjects were <65 y at baseline. No adjustment for potential confounders other than age and gender. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).

* p≤0.05

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; y, year.

For those taking verapamil (n=448), overall cancer risk was not elevated (RR=1.16, 95% CI=0.80-1.62); the report appears to have used the rates of the longitudinal cohort as the comparison. A significant percentage of subjects took beta-blockers, ACE inhibitors, and diuretics, and neither this use nor other potential confounders were addressed in the analyses. Some verapamil users also used other CCBs during follow-up.

Cancer incidence was not increased in those ever prescribed a CCB compared to subjects using other hypertensive drugs (RR=1.02, 95% CI=0.82-1.27); comparison with the external control groups gave nearly identical values. For use of any CCB, the authors reported statistically significant elevated site-specific rate ratios for kidney (RR=2.15, p<0.01) and skin (RR=1.56, p<0.05) cancer; breast cancer was elevated but not significantly (RR=1.45, p>0.05). The methodology used in these calculations was unusual, incorporating both rates in non-CCB users and in the general population.

Table 5: Study comparing cancer risk in cohort using verapamil with rates in another cohort studied previously

Study author **Cohort characteristics**	**Exposure and outcome definition**	**Exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Hole *et al.*, 1998 2297 CCB users in Glasgow, Scotland. Total exposed to verapamil, n=448. <u>*Cohort*</u> <u>Age</u>: no limits, avg age:men, 54.7 y women, 57.4 y. <u>Gender</u>: 50.8% male <u>Comparison:</u> A different cohort from two towns near Glasgow, surveyed in 1972-76.	**Any use of verapamil** All cancer	34	1.16 (0.80-1.62)	Use of multiple CCBs included. No information on duration of use. Avg follow-up, 5 y. Adjusted for age, gender and smoking status, but not for other potential confounders. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors). For comparisons other than specific CCBs, general population rates were used.

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; CCB, calcium channel blocker; CI, confidence interval; y, year.

Case-control studies

Jick et al., 1997

Jick *et al.* (1997) conducted a nested case-control analysis of data from a cohort of users of CCBs, ACE inhibitors and beta-blockers, identifying all cases of cancer diagnosed in 1995 (Table 6). The study included 446 cases and 1750 controls. Information was obtained from an ongoing data collection effort, the General Practice Research Database (GPRD) in the United Kingdom, including prescription details and diagnoses, as well as demographic information and smoking status. Study subjects were limited to those who had at least four years of continuous medical history in the GPRD. To be included, the subjects had to have taken no more than one of the study drugs during the year before the index date (case, cancer diagnosis date; control, matched case's index date). Information on time since first exposure was not collected, although duration of use was assessed. Controls (up to four per case) were hypertensive subjects who did not have cancer, matched to the case for age, gender, and the general practice they attended. Cancer incidence was based on hospital admission.

In the analyses of cancer risk, the investigators adjusted for smoking, BMI, change of medication, duration of hypertension, and diuretic use. Users of beta-blockers served as the exposure reference group (n=938). Verapamil use (number exposed not specified) was associated with an increased overall cancer risk that approached but did not reach statistical significance at the 0.05 level (odds ratio, OR=1.83, 95% CI=0.94-3.56). No analysis of verapamil use by dose, duration or site-specific cancer was presented.

For subjects using any calcium channel blocker, risk of overall cancer did not appear to increase with increasing duration of CCB use (<1 year, OR=1.46; 1.0-3.9 years, OR=1.26; ≥4 years OR= 1.23; p>0.05 for each). There was, however, some indication of increasing overall cancer risk with increasing dose of CCB (low, OR=1.21; intermediate, OR=1.17; high, OR= 1.71, p<0.05). Of the site-specific cancer risks with CCB use provided in the report, the highest were lung, bowel, and breast (ORs 2.22, 1.41, and 1.32, respectively); none were statistically significant.

Rosenberg et al., 1998

Rosenberg *et al.* (1998) conducted a case-control study of cancer and CCB use, based on 9513 subjects admitted for first cancer diagnosis to a hospital, encompassing several hospitals in the northeastern U.S. (Massachusetts, New York, Pennsylvania and Maryland) (Table 6). Controls were 6492 subjects admitted to these same hospitals for a variety of other conditions; control selection excluded those admitted for conditions related to anti-hypertensive drug use, e.g., cardiovascular diseases. Data were collected during 1983-1996, with study participants limited to those less than 70 years of age. Information on when use of CCBs began was taken into account in the analyses, although data on doses were lacking. Multiple logistic regression models included variables for age (five-year categories), race, years of education, pack-years of smoking, BMI, and annual physician visits for all cancer analyses, with additional variables for site-specific analyses.

Risks were presented for those who began using verapamil more than one year before admission to the hospital, and average duration of use (of any CCB) was 3.8 years. Verapamil use of any duration led to a risk for overall cancer incidence of 1.2 (95% CI=0.9-1.5). For those who used verapamil more than five years, the cancer risk was similar (OR=1.1, 95% CI=0.7-1.8). No site-specific cancer results were presented for verapamil.

The risk associated with any CCB varied by duration of use, increasing slightly with increasing years of use (<1 year, OR=0.8, 95% CI=0.4-1.5; 1-4 years, OR=1.1, 95% CI=0.9-1.3; ≥5 years, OR=1.2, 95% CI=0.9-1.5), although none of these reached statistical significance. Elevated risks of kidney (OR=1.8, $p \leq 0.05$), esophageal (OR=1.8, $p>0.05$), and respiratory (non-lung) cancer (OR=1.7, $p>0.05$), as well as malignant melanoma (OR=1.6, $p>0.05$) were seen with any CCB use, with kidney cancer being statistically significant. For those with more than five years of CCB use, colon cancer risk was significantly elevated (OR=1.7, 95% CI=1.0-2.8). Other elevated site-specific risks in those exposed at least five years to any CCB included kidney (OR=1.9, 95% CI=0.9-3.9) and pancreatic cancer (OR=1.8, 95% CI=0.8-4.0), and malignant melanoma (OR=1.7, no CI provided, three cases), although these did not reached statistical significance, and the numbers of exposed cases were small.

Hardell et al., 1996

In a case-control study in Sweden, Hardell *et al.* (1996) reported on previous diseases and drug intake associated with colon cancer, examining 301 cases and 621 population controls (Table 7). Information was collected by mailed questionnaire, supplemented by follow-up telephone contact. No information was collected on time since first exposure to the agents assessed in this study. Controls were found using the national population register, matched for gender, age and county, two per case. While various diseases and drugs were found to be associated with colon cancer, the highest increase in risk was associated with verapamil intake (OR=22, 95% CI=2.4-480, based on 10 cases and one control). The exposure referent category included all those who did not use verapamil. Hypertension and use of beta-blockers were also examined as independent risk factors for colon cancer, and neither was associated with an increased risk. Although this hypothesis-generating study of potential risk factors for colon cancer is far from definitive, and did not control for many factors of interest, the strength of the association found for verapamil is striking.

Meier et al., 2000

Meier *et al.* (2000) conducted a case-control study of 3706 post-menopausal women with breast cancer, aged 50 years or older, approximately 42% of whom were 70 years or older (Table 7). These women were matched to 14,155 controls by age, physician practice, calendar date (the same as index date), and number of years of medical history recorded in the GPRD as described in summary above of Jick *et al.* (1997) (all of Meier *et al.* authors were also authors of that study). For subjects in the study, the mean duration of GPRD medical history was 5.3 years prior to the index date (range, 3-14 years). Women with less than three years of medical history in the GPRD prior to the index date were excluded. Duration of CCB use was unknown for 20%

Table 6: Case-control studies of verapamil use and overall cancer risk

Study author **Case-control characteristics**	**Exposure and outcome definition**	**Verapamil-exposed cancer cases**	**Odds ratio (95% CI)**	**Comments**
Jick *et al.*, 1997 446 cases and 1750 controls in the UK. Age limit: none, avg age 71.6 y Gender: 50.5% male *Verapamil analysis* Cases:14 exp, 183 unexposed Controls: exp NA, 755 unexposed Exposure referent: Use of beta blockers	**Any use of verapamil ≥1 y before diagnosis** All cancer	14	1.83 (0.94-3.56)	Single CCB therapy only, and exposure referent was those who used only beta-blockers. Controls were hypertensives, matched to cases on age, gender, and general practice attended. Drug exposure information available from ≥4 y before diagnosis, based on general practitioners' prescriptions database. Analyses control for smoking, BMI, and other potential confounders.
Rosenberg *et al.*, 1998 9513 persons first admitted to hospitals for first cancer compared to 6492 persons admitted for other conditions. Age limit: <70 y, avg age 56 y Gender: 41% male *Verapamil analysis* Cases: 172 exp, 8855 unexposed Controls:111 exp, 6011 unexposed Exposure referent: Never used CCBs	**Any use of verapamil beginning ≥1 y before admission** All cancer **Verapamil use lasted ≥5 y and began ≥1 y before hospital admission** All cancer	172 51	1.2 (0.9-1.5) 1.1 (0.7-1.8)	Control selection excluded those admitted for conditions related to anti-hypertensive drug use, e.g., cardiovascular diseases. Exposure data, including duration of use, collected in hospital interviews. Models included age (5-y), race, y of education, smoking pack-y, BMI, and annual physician visits, but no control for multiple CCBs or other drugs.

Abbreviations: avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; exp, exposed; NA, not available; y, year.

Table 7: Case-control studies of verapamil use and site-specific cancer risk

Study author **Case-control characteristics**	**Cancer site and exposure**	**Verapamil -exposed cancer cases**	**Odds ratio (95% CI)**	**Comments**
Hardell *et al.*, 1996 301 cases and 621 population controls in Sweden Age limit: none avg age not given Gender: 50% male *Verapamil analysis* Cases: 10 exposed, 291 unexposed Controls: 1 exposed, 620 unexposed Exposure referent: No verapamil use	Colon **Any use of verapamil**	 10	 22* (2.4-480)	A relatively small number of exposed cases, and only one exposed control. Drug use self-reported on questionnaire. No analysis of duration of use. No control for potential confounders other than gender, age and county. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).
Meier *et al.*, 2000 3706 women, 14,155 controls in the UK Age: ≥50 years old, avg age not given. Gender: 0% male *Verapamil analysis* Cases: 23 exposed, 2567 unexposed Controls: 64 exposed, 9745 unexposed Exposure referent: No use of anti-hypertensive drugs	Breast **1-2 y of verapamil use** **3-4 y of verapamil use** **≥ 5 y of verapamil use**	 8 4 7	 1.6 (0.7-3.7) 4.0* (1.0-16.1) 1.0 (0.4-2.4)	Single drug anti-hypertensive therapy only. Drug exposure available from ≤3 y before diagnosis, based on prescription database. Duration of avg CCB use not specified, unknown for 20% of cases using CCBs. Controls matched on age, physician practice, index date, and number of y medical history. Risk estimates adjusted for smoking and BMI.

*p≤0.05

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; y, year.

of the cases who had used CCBs. Length of time since first use of CCBs was not reported, nor was any information on cumulative dose.

Risks of breast cancer were calculated by comparing those who used verapamil with those who did not use any antihypertensive drugs (including beta blockers and ACE inhibitors), adjusting for smoking status and BMI. Included in the verapamil odds ratio were 2590 cases and 9809 controls. The risks seen with verapamil use were elevated for the shortest and mid-length duration categories, the latter significantly (1-2 years: OR=1.6, 95% CI=0.7-3.7; 3-4 years: OR=4.0, 95% CI=1.0-16.1), but not for those with the longest exposure duration (≥5 years: OR=1.0, 95% CI=0.4-2.4).

Use of any CCB was not associated with an increased risk of breast cancer (Table 9), regardless of the duration of use (1-2 years: OR=1.0, 95% CI=0.8-1.3; 3-4 years: OR=1.0, 95% CI=0.6-1.6; ≥5 years: OR=0.9, 95% CI=0.7-1.2). For specific CCBs other than verapamil, no elevated risks were seen for any duration of use.

Discussion

In examining the potential for verapamil to cause cancer in humans, several important aspects need to be considered. One is the quality of the studies which have assessed the association of verapamil exposure with cancer. Another is the strength of the observed association. The reproducibility of the effect in multiple populations is another consideration, especially in those studies that have adequate control for potential confounding. Indications of a dose-response for the effect are also important. These points are considered below with respect to results seen in the available studies. As little is currently known about how verapamil might increase cancer risk in individuals taking this drug, it is unclear which specific cancer sites or tissues might be expected to be affected. Thus, to assess the evidence of carcinogenicity, verapamil-specific increased risks for both for overall cancer and specific sites are discussed. Results for any CCB exposure in these studies are also briefly considered, to the extent that they supply additional information on certain issues.

Study quality

Adequate control for confounding is a critical aspect of study quality in assessing the evidence for verapamil carcinogenicity in these studies. Factors leading to hypertension and coronary artery disease, conditions treated with CCBs including verapamil, may also be associated with an increased risk of cancer. Thus, adequate control in studies of factors such as smoking, alcohol intake, use of other prescription drugs (to treat hypertension and coronary artery disease), as well as control for other indications of health status such as number of hospital admissions, allows for a clearer assessment of the potential contribution to cancer risk being made by verapamil exposure. Only three of the available studies adequately addressed all of these issues and provided verapamil-specific risk estimates (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al.*, 2003; Jick *et al.*, 1997). A few studies attempted to address the issues but were limited by the number of verapamil-exposed study subjects in their analyses and/or the length of follow-up (Fitzpatrick *et al.*, 1997; Braun *et al.*, 1998; Cohen *et al.*, 2000). Other studies addressed some but not all of these issues (Rosenberg *et al.*, 1998; Meier *et al.*, 2000) and still others addressed them only minimally (Hardell *et al.*, 1996; Olsen *et al.*, 1997a; Hole *et al.*, 1998; Sajadieh *et al.*, 1999).

Another important aspect of study quality is the completeness of the exposure data, the manner in which exposure was defined, and how thoroughly investigators distinguished between those exposed and those not exposed. The best cohort study (Beiderbeck-Noll *et al.*, 2003) not only adequately controlled for factors that may influence cancer risk, but also used multiple sources of information on exposure (three sets of in-person interviews at two- to three-year intervals, which included examination of bottle labels, as well as use of data from pharmacy prescription databases) to ascertain exposure to verapamil in a way that reduced potential exposure misclassification. Pharmacy or physician database records were also used in some other studies (Jick *et al.*, 1997; Olsen *et al.*, 1997a; Rosenberg *et al.*, 1998; Meier *et al.*, 2000), while a few other studies had multiple in-person interviews that verified continued use (Fitzpatrick *et al.*, 1997; Cohen *et al.*, 2000). Studies by Jick *et al.* (1997) and Meier *et al.* (2000) defined exposure as use of a single CCB based on physician records and limited the study to those with multiple years of medical history. Pahor *et al.* (1996a and 1996b) recorded verapamil use at the time of interview in 1988, but did not use information available for the cohort on previous exposure, or collect any information on subsequent exposure. Other studies failed to distinguish between subjects with a single verapamil prescription and those who had taken it daily for years (e.g., Olsen *et al.*, 1997a; Braun *et al.*, 1998; Hole *et al.*, 1998); another had subjects with one year of verapamil use and no information on subsequent exposure (Sajadieh *et al.*, 1999). Such studies may have misclassified the exposure of substantial proportions of their study subjects.

Cancer is a multi-stage process, often taking years following a carcinogenic exposure for a cancer to be expressed. A third aspect of study quality is the extent to which information on latency, or the length of time from first exposure to onset of cancer, is available to determine whether an observed effect is biologically plausible. Available studies of verapamil do not provide adequate data to assess risk by time since first exposure. Many studies did not collect data on the amount of time elapsing between initial exposure and cancer diagnosis. Some studies restricted analyses to those with exposure at least one year prior to diagnosis (Fitzpatrick *et al.*, 1997; Rosenberg *et al.*, 1998), and one study separately analyzed those with two or fewer and more than two years of exposure prior to diagnosis (Beiderbeck-Noll *et al.*, 2003). Studies which had information regarding the date verapamil use was initiated (Jick *et al.*, 1997; Rosenberg *et al.*, 1998; Sajadieh *et al.*, 1999; Beiderbeck-Noll *et al.*, 2003) did not analyze risk in relation to this variable. Several studies did not distinguish use that had begun within the same year as diagnosis from use that had begun earlier (Pahor *et al.*, 1996a and 1996b; Hardell *et al.*, 1996; Olsen *et al.*, 1997a).

Increased overall and site-specific cancer risks with verapamil exposure

The strength and consistency of the observed associations of cancer risk with verapamil exposure are relevant to the consideration of its potential carcinogenicity. Increased risk of overall cancer after verapamil exposure was statistically significant in the two cohort studies with the best control of confounding (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al.*, 2003). Both of these studied elderly subjects who were predominantly female. Also, in the case-control study with the best control of confounding (Jick *et al.*, 1997), overall cancer risk was elevated but did not reach statistical significance. In this study, subjects were also elderly but gender-balanced. In these studies with the best control of confounding (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al*., 2003; Jick *et al*., 1997), an approximate doubling of the relative risk was seen with verapamil exposure. Several other studies, which lacked adequate control for potential confounders or had other substantial weaknesses, all had similar estimates of overall cancer risk (around 1.2) (Rosenberg *et al.*, 1998; Braun *et al.*, 1998; Hole *et al.*, 1998; Cohen *et al.*, 2000). The two studies comparing rates in exposed cohorts with general population rates found no elevated overall cancer risk (Olsen *et al.*, 1997a; Sajadieh *et al.*, 1999). These two studies had significant potential for exposure misclassification, with one study having very short follow-up time from identifying exposure to determining outcome (Olsen *et al.*, 1997a) and the other lacking information on exposure during years following a clinical trial (Sajadieh *et al.*, 1999). Information on average age in these last two studies was not presented, but the latter one was predominantly male. In all of the studies which examined both verapamil and any CCB exposure, point estimates of overall cancer risk for verapamil exposure were higher than those for any CCB exposure.

Unrelated to any of these studies, Dong *et al.* (1997) performed a meta-analysis of published randomized, controlled trials of verapamil, identifying 39 trials of which only five reported any cancer cases (n=34 cases); the authors assumed no reported cancers meant no cancers had occurred. Overall risk of cancer and cancers deaths after verapamil exposure was not elevated compared to active controls (persons taking other drugs to control hypertension or coronary artery disease) (OR=1.20, 95% CI=0.60-2.42) or compared to those given a placebo (OR=0.73, 95% CI=0.39-1.39) (Dong *et al.*, 1997). The results of this meta-analysis are difficult to interpret given the relatively short duration of exposure to verapamil in most trials (average, 29.5 weeks, median 12 weeks), and the fact that all cancer cases may not have been identified because of the number of trials (12 of 39) which had inadequate follow-up, and the lack of information on patient demographics (e.g., smoking status) which precluded exploration of those cases that were identified.

With respect to specific cancer sites, only a few studies had adequate numbers to examine these in relation to verapamil exposure (Tables 1 - 7), and the strength of the association seen varies by study and cancer site. Results discussed are based on more than five exposed cases, unless otherwise stated. Statistically significant elevated risks with verapamil use were found in cohort studies for cancers of the respiratory system (Sajadieh *et al.*, 1999) and lymphatic and hematopoietic tissues (Beiderbeck-Noll *et al.*, 2003). Case-control studies found significantly increased risks with verapamil use for breast (Meier *et al.*, 2000) and colon cancer (Hardell *et al.*, 1996). Due to issues of study quality, some findings are more compelling than others.

Significantly increased risk of LHC (9^{th} International classification of diseases (ICD-9) codes 200-208) (RR=7.84, number of cases not specified) was seen in verapamil users in the best study conducted to date, the prospective cohort study of Beiderbeck-Noll *et al.* (2003). These authors noted that risks of specific cancers associated with verapamil use were generally higher than those associated with any CCB use (see values for any CCB use, reported below), but they reported only the statistically significant elevated risk associated with LHC. The limited cohort study by Sajadieh *et al.* (1999) found a statistically significant elevated risk of respiratory cancer in women (SIR=3.9, based on five cases) but had no control for smoking; risk in men in this study (SIR=0.8) was not elevated.

In the well-designed case-control study focused on breast cancer (Meier *et al.*, 2000), risks for verapamil users were increased and there was an indication of a dose-response, with statistically significant elevated risks for those with three to four years of exposure (1-2 years, OR=1.6; 3-4 years, OR=4.0, $p \leq 0.05$, based on four exposed cases; ≥5 years, OR=1.0). The cohort study by Fitzpatrick *et al.* (1997), a well-designed study in older women with small numbers of verapamil-exposed breast cancer cases, provides some support for this association, with high unadjusted breast cancer rates in those using one type of verapamil formulation but not the other (discussed below under *Dose-response effects*). The case-control study of colon cancer (Hardell *et al.*, 1996) found highly elevated statistically significant risks (OR=22) for verapamil users, although this study lacked control for confounding, and the confidence interval was wide due to only one exposed person in the control group.

Dose-response effects

Information available on the effect of verapamil dose on cancer risk, both with regard to cumulative exposure and daily dosing, generally indicates a greater risk with greater exposure. Three studies (Beiderbeck-Noll *et al.*, 2003; Rosenberg *et al.*, 1998; Meier *et al.*, 2000) assessed risk in relation to exposure duration, a surrogate for cumulative exposure. Risk of any cancer increased with increasing duration of verapamil exposure in the best study to examine the dose question (Beiderbeck-Noll *et al.*, 2003). The overall cancer risk associated with two or fewer years of verapamil exposure was elevated (RR=1.4, 95% CI=0.8-2.5), and greater than two years verapamil exposure was associated with a significantly elevated risk (RR=2.4, 95% CI=1.2-4.9) (Beiderbeck-Noll *et al.*, 2003). In another study examining duration of exposure, a case-control study (Rosenberg *et al.*, 1998), risk was not increased among a subset who had longer verapamil exposure (≥5 years, RR=1.1, 95% CI=0.7-1.8), and was nearly identical to the risk for any use that had occurred at least one year before hospital admission (RR=1.2, 95% CI=0.9-1.5). The third study with results for verapamil exposure duration, a breast cancer case-control study (Meier *et al.*, 2000), found relative risks of breast cancer were elevated and increased with time exposed for those with the shortest and mid-level exposure durations. Increased breast cancer risks for those with three to four years of exposure were statistically significant (1-2 years, OR=1.6, $p>0.05$; 3-4 years, OR=4.0, $p \leq 0.05$); however, those with the longest duration of use did not have elevated risks (≥5 years, OR=1.0). It should be noted that duration of CCB use was unknown for 20% of the breast cancer cases in the study of Meier *et al.* (2000).

A dose-response effect was apparent in the single study which analyzed the effect of the level of daily verapamil dose on overall cancer risk. Compared to persons who did not use any CCB, Beiderbeck-Noll *et al.* (2003) reported an elevated nonsignificant risk for low defined daily doses of verapamil, and a statistically significant increased risk of cancer for intermediate defined daily doses, and no cases for high defined daily doses (low: RR=1.7, 95% CI=0.7-4.2; intermediate: RR=2.7, 95% CI=1.02-7.4; high: no cases).

Although not strictly the same as comparing different dose levels, a single study (Fitzpatrick *et al.*, 1997) examined the effect on breast cancer risk of different verapamil formulations (immediate release, IR, versus sustained release, SR) in a cohort of women. These formulation differences affect the rate of release of a particular dose into the bloodstream, with SR verapamil providing a slower, more gradual distribution of the drug than IR verapamil. In this study (Fitzpatrick *et al.*, 1997), suggestive differences in unadjusted breast cancer rates were seen, with higher rates among IR verapamil users (IR, 15.7 per 1000 person-years at risk) than SR users, whose rates were similar to those not using CCBs (SR, 4.6 per 1000 person-years at risk; cohort members with no CCB use, 5.1 per 1000 person-years at risk). However, the number of exposed cases was very small, and there was also a difference in the length of time since first exposure between the two exposed groups. The effect of dose formulation needs to be further explored in other studies.

Site-specific results for exposure to any CCB

All of the sites with elevated risk in verapamil-exposed subjects were also elevated in some studies in those with any CCB exposure. Several studies examined specific cancer sites in relation to any CCB exposure (Tables 8 and 9). Multiple reports of elevated risks with any CCB use were made for cancer of the breast (Pahor *et al.*, 1996a; Fitzpatrick *et al.*, 1997; Jick *et al.*, 1997; Hole *et al.*, 1998); colon (Pahor *et al.*, 1996a; Rosenberg *et al.*, 1998; Beiderbeck-Noll *et al.*, 2003) or bowel (Jick *et al.*, 1998) or rectum (Pahor *et al.*, 1996a; Beiderbeck-Noll *et al.*, 2003); lung (Jick *et al.*, 1998; Beiderbeck-Noll *et al.*, 2003); and lymphatic and hematopoietic tissues (Pahor *et al.*, 1996a; Olsen *et al.*, 1997a; Rosenberg *et al.*, 1998; Beiderbeck-Noll *et al.*, 2003). Some but not all of these were statistically significant. Elevated risks were also seen in multiple studies for kidney (Pahor *et al.*, 1996a; Rosenberg *et al.*, 1998; Hole *et al.*, 1998; Beiderbeck *et al.*, 2003) and skin cancer (Hole *et al.*, 1998; Beiderbeck-Noll *et al.*, 2003).

Breast cancer findings have been elevated in all but one of the better studies which looked at site-specific risks in relation to any CCB exposure. Pahor *et al.* (1996a) found a modestly elevated nonsignificant risk (RR=1.65) with any CCB use, in a model that adjusted for estrogen use. Jick *et al.* (1997) found a slightly increased nonsignificant risk (OR=1.32). Fitzpatrick *et al.* (1997) found statistically significant increased risks (HR=2.6) of breast cancer; the association was stronger and retained its significance when CCB use together with estrogen was considered (HR=4.5). In two limited studies, one found an increased risk (Hole *et al.*, 1998: SIR=1.5) with any CCB use, while another did not (Olsen *et al.*, 1997a: SIR=0.8). Breast cancer risks with CCB use were not elevated in the case-control study by Rosenberg *et al.* (1998) (OR=1.1), nor in the case-control study focused on breast cancer, Meier *et al.* (2000) (OR=1.0), in contrast to this study's findings for verapamil-exposed subjects. The best study to date (Beiderbeck-Noll *et al.*, 2003) unfortunately did not calculate breast cancer risks, apparently due to a lack either of exposed or unexposed cases (a total of 20 breast cancer cases occurred in the cohort).

Findings for elevated cancer of the colon, bowel, or rectum were also common in these studies. Pahor *et al.* (1996a) found elevated risks for colon cancer with any CCB use (RR=1.98), which did not reach statistical significance. Rosenberg *et al.* (1998) found a statistically significant increased risk of colon cancer among those who had taken CCBs for more than five years (OR=1.7), but not among those with any use (OR=0.9). The studies which compared CCB users to general population rates without any control for confounders found no increased risks (Hole *et* *al.*, 1998: colorectal, SIR=0.7; Olsen *et al.*, 1997a: colon, SIR=0.8). In their case-control study, Jick *et al.* (1997) reported a slightly elevated risk for bowel cancer with any CCB use (OR=1.4), the same risk level found for colon cancer (RR=1.4) in the cohort study by Beiderbeck-Noll *et al.* (2003), neither of which were statistically significant. Elevated risks of cancer of the rectum were found in both Pahor *et al.* (1996a) (RR=1.32) and Beiderbeck-Noll *et al.* (2003) (RR=2.0), but were not statistically significant or found in other studies.

Lung or respiratory cancer risk was increased in some studies. Increased lung cancer risks with any CCB use reported by Jick *et al.* (1997) (OR=2.2), though not statistically significant, were the highest site-specific risks found in that study, and were adjusted for smoking and based on comparison with rates in other hypertensive subjects. Rosenberg *et al.* (1998) reported statistically nonsignificant elevated risks with any CCB use for respiratory (nonlung) cancer (OR=1.7) in an analysis that adjusted for pack-years of smoking; lung cancer risks were not elevated in this study (OR=1.1 for ≥5 years CCB use). Beiderbeck-Noll *et al.* (2003) found only a slightly increased risk of lung cancer with CCB use (RR=1.3, Model 1), an effect which disappeared entirely in the more extensively controlled analysis (RR=0.8, Model 2).

Increased risks of lymphatic and hematopoietic cancers were seen in several studies. Pahor *et al.* (1996a) found statistically significant increased risks of LHC (ICD-9, codes 200-208) with any CCB use (RR=2.57). Olsen *et al.* (1997a) reported nonsignificant elevated risks for the LHC subcategory non-Hodgkins lymphoma (ICD-7, codes 200, 202) (SIR=1.4), one of the highest SIRs in that study. Rosenberg *et al.* (1998) also found nonsignificant elevated risks for any CCB use for another LHC subcategory, malignant melanoma (OR=1.6; ICD version and codes not specified), and the risk remained elevated in those exposed longer (≥5 years, OR=1.7, based on three exposed cases). The prospective study of Beiderbeck-Noll *et al.* (2003) found users of any CCB (including verapamil) had nonsignificant elevated risks of LHC (ICD-9, 200-208) (RR=2.0), much lower than the significantly elevated risks seen in verapamil users in the cohort.

Multiple reports of increased cancer of the kidney were made for any CCB use (Pahor *et al.*, 1996a; Rosenberg *et al.*, 1998; Hole *et al.*, 1998; Beiderbeck *et al.*, 2003). Kidney cancer findings in the Rosenberg *et al.* (1998) study were questioned by Messerli and Grossman (1998), who noted that renal cell cancer may be related to diuretic use. They indicated that the target site for the pharmacologic effect of diuretics, the renal tubular cell, is the place from which this cancer arises. Rosenberg *et al.*'s findings for this site (OR=1.8) were statistically significant, while findings by Pahor *et al.* (1996a) (RR=1.57), Hole *et al.* (1998) (SIR=2.2) and Beiderbeck-Noll *et al.* (2003) (RR=1.5) were not. The similarity of the risk estimates for the two studies which controlled for diuretic use in examining risks (Pahor *et al.*, 1996a; Beiderbeck-Noll *et al.*, 2003) is notable; these two studies also reported the results in a grouping (bladder, ureter, kidney) which differed from the others.

Skin cancer was increased in two studies (Hole *et al.*, 1998; Beiderbeck-Noll *et al.*, 2003). La Vecchia and Bosetti (2003) questioned findings of statistically significant elevated skin cancer in the Beiderbeck-Noll *et al.* (2003) study (RR=2.7), and suggested its incidence was influenced by diagnostic attention that they believe may be greater in those under long-term drug treatment (i.e., CCB users). Hole *et al.*'s findings for skin cancer (SIR=1.6) were not statistically significant, and given the limitations of that study provide no strong support for an effect.

Summary

Epidemiologic studies of subjects taking verapamil on the whole report an increased overall risk of cancer, although significantly increased risks were found only in a few studies. Overall cancer risk was approximately doubled in the studies that best controlled for potential confounding (Beiderbeck-Noll *et al.*, 2003; Pahor *et al.*, 1996a and 1996b; Jick *et al.*, 1997). Increased risk of LHC with verapamil exposure was seen in the best cohort study (Beiderbeck-Noll *et al.*, 2003). A well-designed breast cancer case-control study (Meier *et al.*, 2000) found increased risks with verapamil exposure, while a case-control study with a more limited design found a strong indication of increased colon cancer risk with verapamil exposure (Hardell *et al.*, 1996). Findings for these cancer sites for verapamil-exposed subjects are consistent with results in some but not all studies which examined site-specific results only for subjects exposed to any CCB (including verapamil). In addition, evidence of a dose-response effect with verapamil exposure was seen for overall cancer risk and exposure duration (as a measure of cumulative exposure) as well as for overall cancer risk and daily dose level in the best, most recently conducted study (Beiderbeck-Noll *et al.*, 2003). The breast cancer case-control study also reported an effect of dose in terms of duration of exposure (Meier *et al.*, 2000).

Table 8: Any calcium channel blocker use and site-specific cancer risk: Cohort studies in chronological order

Study author Cohort characteristics	Cancer site and exposure	Cancer cases	Relative Risk estimate (95% CI)	Comments
Pahor *et al.*, 1996a 5052 persons from U.S., 3 regions *Cohort* Age: ≥ 71 y, avg age 79.0. Gender:35.9% male Comparison: within cohort to non-CCB users	**Any CCB use** Stomach Colon Rectum Breast Uterus Prostate Bladder, ureter, kidney Lymphatic & hematopoietic tissues	 13 65 23 31 23 58 38 46	 3.64 (0.96-13.76) 1.98 (0.90-4.38) 1.32 (0.31-5.74) 1.65 (0.49-5.55) 3.69* (1.22-11.14) 1.99 (0.93-4.27) 1.57 (0.55-4.47) 2.57* (1.13-5.83)	Analyses included those with multiple CCB therapy. Drug use data collected by interview and container label examination. Avg cohort member followed 3.7 y (max: 5 y). Model adjusted for age, gender, ethnicity, smoking, alcohol use, heart failure and number of hospital admissions not related to cancer. No adjustment for concurrent use of other hypertensive drugs. Breast and uterus cancer calculations were adjusted for estrogen use.

Table 8: Any calcium channel blocker use and site-specific cancer risk: Cohort studies in chronological order (continued)

Study author Cohort characteristics	Cancer site and exposure	CCB-exposed cancer cases	Relative Risk estimate (95% CI)	Comments
Fitzpatrick *et al.*, 1997 3198 women, 4 U.S. areas. <u>Cohort</u> <u>Age</u>: ≥ 65 y, avg age 72.9 y. <u>Gender</u>:0% male <u>Comparison</u>: within cohort to non-CCB users	Breast **Any CCB use** **Any CCB & estrogen use** **IR CCB & estrogen use**	20 4 4	2.6* (1.5-4.5) 4.5* (1.6-12.8) 8.5* (3.0-24.1)	Controls were cohort members using no CCBs. For estrogen use, comparison was with those using no estrogen or CCB. Up to 5 y follow-up. Avg length of CCB use varied from 2.7-3.9 y. IR users had longer follow-up, avg 3.9 y.
Hole *et al.*, 1998 2297 CCB users in Glasgow, Scotland. <u>Cohort</u> <u>Age</u>: no limits, avg age:men, 54.7 y women, 57.4 y. <u>Gender</u>: 50.8% male <u>Comparison:</u> General population rates and comparison to those in cohort not on antihypertensives.	**Any CCB use** Kidney Skin Breast	9 26 14	2.2 (NA) 1.6 (NA) 1.5 (NA)	Use of multiple CCBs included. No information on duration of use. Avg follow-up, 5 y. Adjusted for age, gender and smoking status, but not for other potential confounders. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors). Unusual calculation for relative risks used for these analyses. See text.

Table 8: Any calcium channel blocker use and site-specific cancer risk: Cohort studies in chronological order (continued)

Study author **Cohort characteristics**	**Cancer site and exposure**	**CCB-exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Olsen *et al.*, 1997a 17,911 CCB users in a county in Denmark. Total exposed to verapamil, n=4879. *Cohort* Age: no limits, avg age not given Gender: 49% male Comparison: general population.	**Any CCB use** LHC (ICD7: 200-205) Non-Hodgkins lymphoma (ICD7:200, 202) Urinary bladder Brain	 34 17 47 14	 1.1 ((0.8-1.6) 1.4 (0.8-2.2) 1.5 (1.1-2.1) 1.5 (0.8-2.5)	Use of multiple CCBs included. Pharmacy database provided drug use information. Very short follow-up (≤3 y; avg 1.8 y). No adjustment for potential confounders other than age and gender. No adjustment for concurrent use of other anti-hypertensive drugs (e.g., ACE inhibitors).
Beiderbeck-Noll *et al.*, 2003 3204 persons in Rotterdam, the Netherlands. *Cohort* Age: ≥71y, avg age 79.2. Gender:35.5% male Comparison: within cohort to non-CCB users	**Any CCB use** Skin Liver, gallbladder, & pancreas Lung Bladder, ureter & kidney Colon Rectum Lymphatic & hematopoietic tissues	 26 10 24 26 43 16 15	 2.7* (1.03-7.3) 3.1 (0.6-14.9) 1.3 (0.3-5.5) 1.5 (0.5-5.1) 1.4 (0.5-3.8) 2.0 (0.5-8.8) 2.0 (0.4-8.9)	Single CCB therapy only. Information on drug dosage from container label examined during interview. Median cumulative exposure to CCBs: 2 y. Max follow up 8 y. Values listed were calculated using Model 1, which adjusted for: age, gender, heart failure, smoking status, hospital admissions, alcohol intake.

*p≤0.05

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; IR, immediate release; NA, not available; y, year.

Table 9: Any calcium channel blocker use and site-specific cancer risk: Case-control studies in chronological order

Study author Case-control characteristics	Cancer site and exposure	CCB-exposed cancer cases	Relative Risk estimate (95% CI)	Comments
Jick *et al.*, 1997 446 cases and 1750 population controls in the UK. *Cases* Age limit: none, avg age 71.6 y Gender: 50.5% male	**Any CCB use** Lung Bowel Breast	 33^ 59^ 80^	 2.22 (0.76-6.55) 1.41 (0.65-3.06) 1.32 (0.72-2.41)	Single CCB therapy only. Controls were hypertensives, matched to cases on age, gender, and general practice attended. Information on drug exposure available from ≥4 y before diagnosis, based on prescription database. Analyses control for smoking, BMI, and other potential confounders.
Rosenberg *et al.*, 1998 9513 persons admitted to hospitals for first cancer compared to 6492 persons admitted for other conditions. *Cases* Age limit: <70 y, avg age 56 y Gender: 41% male	**CCB use** Kidney **- any use** **- ≥ 5 y use** Colon **- any use** **- ≥ 5 y use** Respiratory (non-lung) **- any use** **- ≥ 5 y use** Malignant melanoma **- any use** **- ≥ 5 y use**	 31 9 46 20 5 1 16 3	 1.8* (1.1-2.7) 1.9 (0.9-3.9) 0.9 (0.7-1.3) 1.7* (1.0-2.8) 1.7 (0.6-4.7) 1.3 (NA) 1.6 (0.8-3.0) 1.7 (NA)	Control selection excluded those admitted for conditions related to anti-hypertensive drug use, e.g., cardiovascular diseases. Exposure data, including duration of use, collected in hospital interviews. Models included age (5-y), race, y of education, smoking pack-y, BMI, and annual physician visits, but no control for multiple CCBs or other drugs.

Table 9: Any calcium channel blocker use and site-specific cancer risk: Case-control studies in chronological order (continued)

Study author **Case-control characteristics**	**Cancer site and exposure**	**CCB-exposed cancer cases**	**Relative Risk estimate (95% CI)**	**Comments**
Meier *et al.*, 2000 3706 women, 14,155 controls in the UK. *Cases* Age: ≥50 years old, avg age not given. Gender: 0% male	**Any CCB** Breast cancer - **1-2 y use** - **3-4 y use** - **≥ 5 y use**	 79 19 53	 1.0 (0.8-1.3) 1.0 (0.6-1.6) 0.9 (0.7-1.2)	Single drug anti-hypertensive therapy only. Drug exposure available from ≤3 y before diagnosis, based on prescription database. Duration of avg CCB use not specified, unknown for 20% of cases using CCBs. Controls matched on age, physician practice, index date, and number of y medical history. Risk estimates adjusted for smoking and BMI.

* p≤0.05
^ Cases listed include both exposed and unexposed

Abbreviations: ACE, angiotensin-converting enzyme; avg, average; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; NA, not available; y, year.

3.2 Carcinogenicity Studies in Animals

Carcinogenicity studies in rats as discussed in the Physician's Desk Reference entry for verapamil hydrochloride (Covera-HS®) are summarized here (PDR, 2004). The study reports were not identified in the published literature, and though information on the studies was requested from the U.S. Food and Drug Administration, no information has been obtained.

> "An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day)."

A few additional bioassays in mice and rats were identified in which verapamil was administered in combination with other agents, generally to investigate its potential for inhibiting carcinogenesis (Satyamoorthy and Perchellet, 1990; Tatsuta *et al.*, 1990; Uehara *et al.*, 1993; Battalora *et al.*, 1995; Nakaizumi *et al.*, 1996; Soybir *et al.*, 1998). None of these studies reported results for a group treated with verapamil alone.

3.3 Other Relevant Data

There has been only limited testing of verapamil in standard tests of genotoxicity. While the mechanism by which verapamil may induce tumors is unknown and little about its properties as a calcium channel blocker suggests carcinogenic potential, some data have suggested that verapamil may have direct genetic toxicity and synergistically enhance the activity of genotoxic compounds. Another theory that has been advanced is that calcium channel blockers may suppress apoptosis; however, this concept is not well supported in the available scientific literature.

Genotoxicity

Testing of verapamil in five *Salmonella* strains (three milligrams per plate), both with and without metabolic activation, produced no evidence of mutagenicity, although experimental details were not reported, including identification of the strains (PDR, 2004). Verapamil was reported to be not mutagenic in *Salmonella* TA 1537 at concentrations of 50 micromolar (Baguley and Ferguson, 1986).

In vitro, verapamil alone did not induce chromosome or chromatid breaks, chromatid exchanges, or fragments (Nito, 1989) or micronuclei (Liu and Huang, 1997) in Chinese hamster ovary cells. *In vivo* testing in which verapamil was administered by intraperitoneal injection (i.p.) or by oral gavage to either Balb/c or C57BL/6 mice did not result in a clastogenic effect on the bone marrow cells (chromatid breaks or chromosome breaks) (Nesterova *et al.*, 1999).

Verapamil alone did not induce chromosomal aberrations in an *in vitro* assay in human lymphocytes (Scheid *et al.*, 1984). However, in a later study using lymphocytes stimulated with phytohemagglutinin (PHA) from eight human donors, verapamil consistently induced chromosomal aberrations (combined “achromatic lesions (gaps), isochromatid gaps and breaks, interchanges, and acentric fragments”) (Friedman *et al.*, 1990). Co-treatment with the calcium ionophore A23187, which increases intracellular calcium, inhibited the induction of chromosomal aberrations by verapamil, suggesting a role for intracellular calcium in the effect. An *in vivo* portion of this study using PHA-treated lymphocytes from five patients before and after treatment with verapamil for supraventricular tachycardia also showed consistent increases in percentages of mitoses with aberrations. The patient treatment consisted of intravenous administration of five to ten milligrams verapamil followed by 80 milligrams orally three times daily for one week. These authors also reported a “mild and insignificant” increase in chromosomal aberrations among “a few” patients treated with verapamil for more than three years, when compared with “the normal range observed in our laboratory,” although the authors caution against over-interpretation of these results since data were not available for the patients prior to treatment.

Synergy of Verapamil with Genotoxic Agents

In *in vitro* studies published in 1984, verapamil was shown to enhance the cytogenetic effects of the anti-tumor agents bleomycin and peplomycin in human lymphocytes obtained from a single donor, as gauged by increases in dicentric and ring chromosomal aberrations (Scheid *et al.*, 1984). The cytogenetic effects of bleomycin were enhanced by co-treatment with either the calcium channel antagonists verapamil or fendiline (CAS No. 13042-18-7), but not with nifedipine and diltiazem, two other calcium antagonists (reviewed in Scheid *et al.*, 1991). Both verapamil and fendiline are in the diphenylalkylamine class of calcium channel blockers, while nifedipine is a dihydropyridine type calcium channel blocker and diltiazem is a benzothiazapine calcium channel blocker, suggesting the possibility that this effect may be related to the structure of the compounds, rather than their properties as calcium channel blockers.

Oral gavage or i.p. administration of verapamil to Balb/c or C57BL/6 mice significantly increased the clastogenicity of acrylamide, cyclophosphamide, and dioxidine (C57BL/6 mice only) to metaphase bone marrow cells (Nesterova *et al.*, 1999). In Chinese hamster ovary cells *in vitro*, micronuclei were induced by treatment with arsenite (Liu and Huang, 1997). Verapamil potentiated this induction of micronuclei by arsenite.

Verapamil synergistically enhanced the mutagenicity in *Salmonella* (strains TA1537, TA98, and TA100) of known mutagenic compounds from several classes, particularly hydrophobic basic planar polycyclic chromophores (including anilinoacridine anti-tumor drugs, other DNA-binding anti-tumor drugs, acridine derivatives, and at least one hair dye, 4-nitro-*o*-phenylenediamine) (Ferguson and Baguley, 1988). The authors speculated that the enhancement of mutagenicity related to an effect independent of verapamil’s blockage of voltage dependent calcium channels, namely interference with the efflux of such genotoxic compounds from bacterial cells.

In other studies, verapamil enhanced the direct mutagenicity in *Salmonella* of doxorubicin, but did not enhance the mutagenicity of sodium dichromate, 2-methoxy-6-chloro-9[3-(2-chloroethyl)amino-propyl-amino] dihydrochloride (ICR 191), or the S9-mediated mutagenicity of benzo[a]pyrene or 2-amino-3,4-dimethyl-amidazo[4,5-f]quinoline (MeIQ) (De Flora *et al.*, 1997). Among ten coded hair dyes mutagenic in the *Salmonella* assay (strain TA98 or TA100), the addition of verapamil increased the mutagenicity of two (identified only as #28 and #31), decreased the mutagenicity of four, and did not affect the mutagenicity of four (Ferguson *et al.*, 1990).

The cytotoxicity of several drugs to a human sarcoma cell line showed potentiation by verapamil (Harker *et al.*, 1986, abstract only). These authors suggested that "[t]he pattern of sensitization, restricted to agents which produce DNA strand scission by interaction with topoisomerase II, suggests that verapamil may be acting to promote the formation or inhibit the repair of such DNA strand breaks."

A proposed basis for verapamil's ability to potentiate the cytogenetic effect of some chemicals is that verapamil blocks the efflux of genotoxic chemicals, keeping them inside the cell longer, allowing a more robust genotoxic response (the "accumulation hypothesis," discussed in detail by Scheid *et al.*, 1991). It has been suggested that "long-term verapamil therapy could potentially increase the effects of certain environmental mutagens" (Ferguson and Baguley, 1988).

Verapamil and Modulation of Tumorigenicity

Calcium channel blockers have also generally shown the ability to suppress either the growth of cancer cells, or the induction of tumor formation *in vivo* by known carcinogens (reviewed by Mason, 1999a).

Skin papillomas develop in mice initiated by 7,12-dimethylbenz[a]anthracene (DMBA) followed by promotion by tetradecanoylphorbol-13-acetate (TPA) (Satyamoorthy and Perchellet, 1990). When verapamil was also applied to the skin, simultaneous with the application of TPA, the percent of mice with papillomas was significantly decreased. The anti-cancer pharmaceuticals adriamycin and daunomycin were each tested to see if they reduced the incidence of tumors in the DMBA/TPA assay; however, these compounds applied topically did not reduce tumor incidence significantly. Topical treatment with verapamil and adriamycin (or daunomycin) reduced DMBA/TPA tumor induction beyond that seen following topical application of verapamil alone.

In Wistar rats initiated with orally administered *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) followed by promotion with subcutaneously administered caerulein, the incidence of resulting gastric adenocarcinomas was not significantly affected by i.p. co-administration of verapamil (Tatsuta *et al.*, 1990). The incidence of tumors penetrating to the muscle layer was significantly decreased, though. Verapamil treatment alone following MNNG initiation did not influence tumor incidence.

Male Sprague-Dawley rats administered N-nitrosomorpholine in drinking water for eight weeks with verapamil administered i.p. every other day developed fewer hepatocellular carcinomas than those treated with N-nitrosomorpholine alone (10/20 *vs.* 3/20) (Uehara *et al.*, 1993). Body and liver weights were significantly reduced among rats treated with verapamil; the reduction in body weight may have confounded the observed change in tumor incidence.

In SENCAR mice, verapamil induced slight suppression (~20%) of tumor promotion (skin papillomas) by chrysarobin, following initiation by 7,12-dimethylbenz[*a*]anthracene (Battalora *et al.*, 1995).

The induction of glutathione *S*-transferase-positive foci in the pancreas of Wistar rats was considered to be pre-neoplastic (Nakaizumi *et al.*, 1996). These lesions were induced in rats treated with 25 weekly injections of azaserine with alternating day injections of cholecystokinin-octopeptide during and after this treatment. Co-administration of verapamil i.p. in the azaserine/cholecystokinin-octopeptide protocol reduced the number of these lesions in the rats.

Induction of mammary tumors in rats by intravenous injection of 7,12-dimethylbenz[a]anthracene was suppressed by verapamil administered in the drinking water (9/20 *vs*. 3/20) (Soybir *et al.*, 1998). The latency for tumor development also appeared to be increased by verapamil treatment.

Verapamil and Effects on Cellular Growth

A proposed mechanism tying verapamil to processes related to carcinogenicity stemmed from the evolving research relating the calcium channel to the apoptotic process. As a calcium channel blocker, verapamil has been suggested as a potential suppressor of apoptosis. However, a review of the data shows that the effects of calcium channel blockers on apoptosis are mixed, depending on the experimental system used.

Mason (1999a) summarized effects of calcium channel blockers on apoptosis from a number of studies. Systems in which apoptosis is promoted by calcium channel blockers include *in vitro* studies in vascular smooth muscle cells, neuronal cells, colon carcinoma cells, a lymphoma cell line, and a human glioblastoma cell line, and *in vivo* studies of 2-methoxyethanol-induced thymic apoptosis and thymocyte apoptosis in rats. Systems in which apoptosis was inhibited by calcium channel blockers included pancreatic β-islet cells, spermatocytes, prostatic involution, human T cells, and endothelial cells. Regarding studies of verapamil, none has shown the suppression of apoptosis (reviewed by Mason, 1999b; Table 10 below). The overall body of data regarding apoptosis does not lend itself to ready interpretation with respect to the cancer-causing potential of verapamil.

Table 10. Effects of verapamil on cellular growth (Mason, 1999b).

Study	**Effect Observed**
Batra *et al.*, 1991	"Inhibited human prostastic tumor cell growth"
Bertrand *et al.*, 1994	"Inhibited cell growth in a pancreatic cell line stimulated by serum or pentagastrin"
Chang, 1991	"Slightly decreased cell number in a pancreatic tumor cell line"

Study	Effect Observed
Correale *et al.*, 1991	"Promoted lymphokine-activated killer (LAK) induced reduction in human colon and breast cancer cell growth"
Schuller *et al.*, 1991	"Decreased lung cancer (NCI-H358) cell number at doses as low as 1 nmol/liter. No effect on cell lines of Clara and alveolar type II origin."
Shchepotin *et al.*, 1994	"Promoted apoptosis in human primary and metastatic colon adenocarcinoma cell lines"; "decreased human primary and metastatic colon adenocarcinoma cell growth when used in combination with either hyperthermia or 5-fluorouracil"
Taylor and Simpson, 1992	"Inhibited [^{3}H]-thymidine incorporation (cell proliferation) in the breast cancer cell line, HT-39; … verapamil (3.5 mg/day) for two weeks inhibited tumor growth after inoculation of breast cancer cells into athymic nude mice"

Summary

Studies with human lymphocytes have shown clastogenic effects both *in vitro* and *in vivo*, although other studies with other species have not shown such effects. Verapamil alone is not mutagenic in *Salmonella* assays. Verapamil does enhance the effects of certain genotoxic agents in both bacteria and in mammalian cells, and it is not clear whether this effect results from an accumulation of the agent within the cell, or other effects related to the regulation of calcium within the cell. It is also not apparent how this effect should influence the level of carcinogenicity concern, since verapamil has, in several animal studies, had the effect of reducing tumor incidence when co-administered with known carcinogens.

3.4 Pharmacokinetics and Metabolism

The pharmacokinetics and metabolism of verapamil have been briefly reviewed with respect to issues relevant to the potential carcinogenic activity of verapamil, such as differences in bioavailability, elimination and metabolism among various subpopulations. Studies on the tissue distribution of verapamil have also been reviewed. Although verapamil is highly lipophilic, it does not appear to accumulate in fat. Factors which might increase exposure to verapamil and/or specific verapamil metabolites include age, gender, genetic predisposition, and concomitant xenobiotic exposures.

The bioavailability of verapamil is quite low due to extensive first-pass metabolism. Krecic-Shepard *et al.* (2000) reported bioavailability as 20% in men and 25% in women.

Bioavailability is increased in older (> 60 years) individuals (Krecic-Shepard *et al.*, 2000), presumably because of decreased first-pass metabolism, (25% compared to 21%).

Verapamil is administered clinically as a racemic mixture. The R and S enantiomers differ both in their extent of presystemic extraction and their pharmacological potencies. The S enantiomer has greater pharmacological activity and also undergoes preferential first-pass metabolism (Tracy *et al.*, 1999). The R/S ratio of plasma concentrations is about 5 after oral administration (Kroemer *et al.*, 1992).

Maximum plasma concentrations are reached approximately 60 minutes after oral verapamil administration (Krecic-Shepard *et al.*, 2000). Krecic-Shepard *et al.* (2000) measured elimination half-lives in young (mean 26 ± 4 years) and older (mean 70 ± 6 years) individuals (total, 84 individuals). The elimination half-life in younger subjects was 8.1 ± 4 hours after oral verapamil and 6.2 ± 2.8 hours after intravenous (i.v.) administration. Half-lives were increased in older subjects (11.5 ± 5.2 hours after oral verapamil and 8.3 ± 2.8 hours after i.v. administration). Analysis by gender showed that the elimination half-life was longer in women compared to men for both oral and i.v. administration. Plasma protein binding was measured at 91%, and no differences were observed by gender or between older and younger subjects (Krecic-Shepard *et al.*, 2000).

There is little information on tissue distribution after verapamil administration in humans. Distribution of verapamil in cancer patients was studied after i.v. administration of [^{11}C]verapamil (Hendrikese *et al.*, 2001). One hour after injection, 43% of [^{11}C]verapamil had accumulated in the lungs; 1.3% had accumulated in heart tissue. After steady-state i.v. verapamil infusions in dogs, Schwartz *et al.* (1986) also found that verapamil accumulated in the lung. After the lung, the highest concentrations were in the spleen, kidney and liver. There were marked differences in verapamil concentrations in different regions of the heart; accumulation in fat was not observed. In rats, verapamil concentration was measured 30 to 240 minutes after i.p. injection (Hamann *et al.*, 1983). The highest tissue concentration at the time of sacrifice (240 minutes) was again in the lungs, followed by the liver and kidney. Hamann *et al.* (1983) also found that the elimination rate of verapamil varies with different tissues. Of the organs examined in this study, elimination from lung and kidney occurred only half as rapidly as from brain, heart and liver.

Numerous studies published on the *in vivo* and *in vitro* metabolism of verapamil indicate the drug is extensively metabolized. Approximately 70% of an oral dose of verapamil is excreted as metabolites in the urine (Flynn and Pasko, 2000) and less than 5% is excreted as unchanged drug (Kroemer *et al.*, 1992). The predominant biotransformation pathways are N-dealkylation, N-demethylation and O-demethylation (Kroemer *et al.*, 1992; Kroemer *et al.*, 1993; Busse *et al.*, 1995; Tracy *et al.*, 1999). Abernethy *et al.* (2000) measured verapamil metabolites in plasma after a 7-day dosing regimen. The primary metabolites were norverapamil (N-demethylated verapamil), D-617 (N-dealkylation of the phenylethyl moiety), and D-620 (N-demethylation and N-dealkylation of phenylethyl moiety). At least six urinary metabolites, including norverapamil and various N-dealkylated and O-demethylated products, have been identified (Kroemer *et al.*, 1992; Darbar *et al.*, 1998).

The specific cytochrome P450 isozymes involved in the metabolism of verapamil have been identified: Cytochrome P450 3A4 catalyzes the N-demethylation and N-dealkylation of verapamil (Kroemer *et al.,* 1993; Wolbold *et al.*, 2003). Cytochrome P4501A2 also contributes to the formation of norverapamil (Kroemer *et al.,* 1993). Cytochrome P4502C9 is the predominant enzyme catalyzing the O-demethylation of verapamil in human liver (Busse *et al.*, 1995). Cytochrome P450 2C8 and cytochrome P450 2C18 also catalyze verapamil O-demethylation, but they are much less abundant in human liver (Busse *et al.*, 1995).

A significant portion of the first-pass metabolism takes place in the gut wall mucosa (Fromm *et al.*, 1996). Cytochrome P450 3A is the major cytochrome P450 in the human small intestine. Inhibition of intestinal cytochrome P450 3A was shown to increase the plasma concentration of verapamil (Fuhr *et al.*, 2002), and induction of this isozyme was found to markedly decrease verapamil oral bioavailability (Fromm *et al.*, 1996). Cytochrome P450 3A4 is characterized by wide interindividual variability (Paine *et al.,* 1997). The second most prevalent isozyme in the intestinal mucosa, cytochrome P-450 2C, catalyzes the O-demethylation of verapamil (Lapple *et al.*, 2003). This subfamily of enzymes is also characterized by wide interindividual variation and genetic polymorphisms are found in each isozyme of the cytochrome P-450 2C subfamily.

Large interindividual differences in verapamil pharmacokinetics and metabolism have been reported, some of which are clearly related to cytochrome P450 mediated biotransformation. Gender differences in verapamil metabolism have also been observed (Krecic-Shepard *et al.*, 2000; Wolbold *et al.*, 2003). These differences are due in part to higher levels of cytochrome P450 3A4 in women. Wolbold *et al.* (2003) found that cytochrome P450 3A4 levels were 2-fold higher in samples from female human liver samples compared to samples from male livers. N-dealkylation of verapamil was also 50% higher in these same studies. However, there are reports suggesting that verapamil clearance may decrease with age in women to a greater degree than in men (PDR, 2004). The greater bioavailability and longer elimination half-life observed in older compared to younger subjects has been attributed to decreased activities of cytochrome P450 isozymes. In studies comparing verapamil metabolite exposure in older and younger men, Abernethy *et al.* (2000) found that older subjects had a different metabolic profile than younger subjects and greater exposure to verapamil, norverapamil, and the N-dealkylated metabolite D-617.

4 OTHER REVIEWS

The Center for Drug Evaluation and Research in the U.S. Food and Drug Administration (FDA) reviews data submitted by manufacturers prior to approving the use in the U.S. of pharmaceutical products such as verapamil hydrochloride. The summary of the available data on verapamil and verapamil hydrochloride's potential for carcinogenesis provided in the Physician's Desk Reference (PDR, 2004), quoted above (see Section 3.2, Carcinogenicity Studies in Animals), represents the FDA-approved labelling for Covera-HS® (verapamil hydrochloride). Nearly identical language is provided in the 2004 PDR for other prescription drugs containing verapamil hydrochloride (e.g., Isoptin®SR, Verelan®PM, Tarka®). In a literature search and a search of the FDA Internet website OEHHA did not identify any FDA documents that reviewed the carcinogenic activity of verapamil or verapamil hydrochloride.

The carcinogenic activity of verapamil and verapamil hydrochloride do not appear to have been evaluated by the National Toxicology Program, the U.S. Environmental Protection Agency, the National Institutes of Occupational Safety and Health, or the International Agency for Research on Cancer.

5 SUMMARY AND CONCLUSIONS

5.1 Summary of Evidence

The strongest evidence for potential carcinogenicity of verapamil comes from epidemiologic studies. Twelve studies were identified which provided results for verapamil-exposed subjects, including eight cohort (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al.*, 2003; Fitzpatrick *et al.*, 1997; Braun *et al.*, 1998; Cohen *et al.*, 2000; Hole *et al.*, 1998; Olsen *et al.*, 1997a; Sajadieh *et al.*, 1999) and four case-control studies (Jick *et al.*, 1997; Rosenberg *et al.*, 1998; Hardell *et al.*, 1996; Meier *et al.*, 2000). In evaluating this evidence, study quality, the strength of the observed association, the reproducibility of the effect in multiple populations, and indications of a dose-response were taken into consideration in reviewing the results for overall cancer as well as site-specific cancer risk.

The most compelling results come from two cohort studies, both of which compared risks within cohorts of elderly persons (Pahor *et al.*, 1996a and 1996b; Beiderbeck-Noll *et al.*, 2003) and controlled for hypertension and other factors of concern. These studies found significantly elevated risks for overall cancer, showing an approximate doubling of risk in verapamil-exposed subjects. The earliest study to identify the potential for increased risk with CCB exposure, Pahor *et al.* (1996a and 1996b) defined exposure in a way that may have misclassified some individuals. Beiderbeck-Noll *et al.* (2003) replicated the analyses of this initial investigation in a different cohort with similar characteristics, and had rigorous exposure definition as well as more extensive analyses. Beiderbeck-Noll *et al.* (2003) found somewhat lower estimates (RR=2.1, 95% CI=1.1-4.0) than Pahor *et al.* (1996a) (RR=2.49, 95% CI=1.54-4.01) for any use of verapamil and overall cancer risk in the replicated analysis. The later investigators (Beiderbeck-Noll *et al.*, 2003), using much more extensive information on exposure to verapamil, reported elevated overall cancer risk associated with duration of use (≤2 years, RR=1.4, 95% CI=0.8-2.5; >2 years, RR=2.4, 95% CI=1.2-4.9) and daily dose (low: RR=1.7, 95% CI=0.7-4.2; intermediate: RR=2.7, 95% CI=1.02-7.4; high: no cases).

The age and gender distributions of subjects in the cohorts studied by Pahor *et al.* and Beiderbeck-Noll *et al.* may have had some influence on the relative risk estimates, given findings in pharmacokinetic studies that bioavailability is increased in older (>60 years) individuals, and also is somewhat higher in women. Both the cohorts of Pahor *et al.* (1996a and 1996b) and Beiderbeck-Noll *et al.* (2003), from the U.S. and the Netherlands, respectively, were cohorts of older individuals (average age, approximately 79 years) who were predominantly female (approximately 64%). The only other cohort study (Cohen *et al.*, 2000) to compare overall cancer risks in an elderly (average age, 73.4 years), predominately female (65.6%) cohort had a lower overall cancer risk (RR=1.2, 95% CI=0.8-2.2) than that found in Pahor *et al.* (1996a and 1996b) and Beiderbeck-Noll *et al.* (2003). This may be due to a variety of factors, including the use of other CCBs and other anti-hypertensive medications by subjects in Cohen *et al.*, with no control in the analyses for such uses. In addition, the limited number of exposed cases available for analysis may also have reduced the study's ability to detect an effect (numbers not reported, but were noted as being too small to allow for site-specific analyses even for any CCB exposure).

Results seen in Pahor *et al.* (1996a and 1996b) and Beiderbeck-Noll *et al.* (2003) were also not replicated in other cohorts, which had populations somewhat less comparable to those of the studies finding a significantly increased overall cancer risk. Braun *et al.* (1998), studying a mostly male (78%) and younger cohort (average age 59.8 years), and Hole *et al.* (1998), studying a middle-aged (approximate average age, 56 years) cohort with fairly equal gender proportions (50.8% male) had limitations which may have reduced the ability of these studies to find an effect. Both found similar relative risks for overall cancer that were not elevated or significant (Braun *et al.*, 1998 RR=1.16, 95% CI=0.56-2.38; Hole *et al.*, 1998: RR=1.16, 95% CI=0.80-1.62). The Braun *et al.* (1998) study, despite a reasonably large number of exposed subjects, suffered from short observation time (average 34 months) and lacked adjustment for use of other anti-hypertensive drugs. The majority of CCB users in the cohort studied by Hole *et al.* (1998) were not using a CCB three years after it was first prescribed, and cancer rates of the verapamil users were compared with rates in a separate large cohort of persons from a nearby area studied decades earlier (1972-76), rather than a more standard comparison group. A meta-analysis of subjects in clinical trials, limited by small numbers of cancer cases and little information on exposure, found a similar risk (RR=1.2, 95% CI=0.60-2.42) when comparing overall cancer in verapamil-exposed subjects with those taking other hypertensive medications rather than placebo (Dong *et al.*, 1997).

Two studies which compared cancer rates of verapamil users with those of the general population (Olsen *et al.*, 1997a; Sajadieh *et al.*, 1999) found no elevation in relative risks for overall cancer (respectively: SIR=1.09, 95% CI=0.92-1.27; for men, SIR=0.8, 95% CI=0.6-1.1; for women, SIR=0.9, 95% CI=0.4-1.6). Neither study reported the average age of subjects, and while Olsen *et al.* (1997a) was gender-balanced (49% male), Sajadieh *et al.* (1999) was predominantly male (80%). These studies adjusted for age and gender, but did not otherwise address factors of concern. Olsen *et al.* (1997a) suffered from short observation time (average, 1.8 years), and Sajadieh *et al.* (1999) lacked adequate exposure information (no data on exposure during six or more years after an average of 15 months of known exposure), severely limiting the ability of these studies to detect an effect.

Of the two case-control studies of verapamil exposure which considered overall cancer, the one by Jick *et al.* (1997) which compared risks within groups of hypertensive subjects found a nonsignificant relative risk (OR=1.83, 95% CI=0.94-3.56) fairly close to that seen in Beiderbeck-Noll *et al.* (2003). Jick *et al.* (1997) included subjects who were older (average age 71.6 years) and gender balanced (50.5% male). This study had the strengths of having defined exposure as use of a single CCB based on physician records and limited the study to those with multiple years of medical history. The other case-control study which examined overall cancer risk (Rosenberg *et al.*, 1998) found a lower risk estimate, again not statistically significant, similar to that found in the limited cohort studies (OR=1.2, 95% CI=0.9-1.5). This study used hospital-based subject selection, with controls excluding those admitted for conditions related to anti-hypertensive drug use; the authors did not address concurrent use of anti-hypertensive drugs in the analyses. Although this study, whose subjects were middle-aged (average, 56 years) and a majority female (59%), had the strength of requiring use at least 12 months prior to hospital admission, longer duration of use was not associated with an increase in overall cancer risk in verapamil users (≥5 years, OR=1.1, 95% CI=0.7-1.8).

Only a few studies had adequate numbers to examine site-specific cancer rates in relation to verapamil exposure. The best designed cohort study found statistically significant increased risk for lymphatic and hematopoietic cancer (Beiderbeck-Noll *et al.*, 2003: RR=7.84, 95% CI=1.66-37.0). The limited cohort study by Sajadieh *et al.* (1999) found a statistically significant elevated risk of respiratory cancer in women (SIR=3.9, 95% CI=1.3-9.1, based on five exposed cases) but had no control for smoking. Statistically significant elevated risks with verapamil use were found in a case- control study of breast cancer in post-menopausal women (Meier *et al.*, 2000: 1-2 years, OR=1.6, 95% CI=0.7-3.7; 3-4 years, OR=4.0, 95% CI=1.0-16.1, based on four exposed cases; ≥5 years, OR=1.0, 95% CI=0.4-2.4). A case-control study of colon cancer with a more limited design (Hardell *et al.*, 1996) found a significantly elevated risk (OR=22, 95% CI=2.4-480).

All of these tumor sites elevated in verapamil-exposed subjects were also elevated in some studies in those with any CCB exposure (including verapamil). Breast cancer risks were elevated in all but one of the better studies which looked at site-specific risks in relation to any CCB exposure, including: Pahor *et al.* (1996a: RR=1.65, 95% CI=0.49-5.55), in a model that adjusted for estrogen use); Jick *et al.* (1997: OR=1.32, 95% CI=0.72-2.42); and Fitzpatrick *et al.* (1997: HR=2.6, 95% CI=1.5-4.5; use together with estrogen: HR=4.5, 95% CI=1.6-12.8). Breast cancer risks with CCB use were not elevated in the case-control study by Rosenberg *et al.* (1998) (OR=1.1, 95% CI=0.8-1.4). Findings for elevated cancer of the colon, bowel, or rectum were also common in these studies: Pahor *et al.* (1996a: colon cancer, RR=1.98, 95% CI=0.90-4.38; rectum cancer, RR=1.32, 95% CI=0.31-5.74); Rosenberg *et al.* (1998: colon cancer ≥5 years use, OR=1.7, 95% CI=1.0-2.8); Jick *et al.* (1997: bowel cancer, OR=1.4, 95% CI=0.65-3.06); and Beiderbeck-Noll *et al.* (2003: colon cancer, RR=1.4, 95% CI=0.5-3.8; rectum, RR=2.0, 95% CI=0.5-8.8). Lung or respiratory cancer risk was increased in some studies, including Jick *et al.* (1997: OR=2.2, 95% CI=0.76-6.55, adjusted for smoking); Rosenberg *et al.* (1998: respiratory (nonlung) cancer, OR=1.7, 95% CI=0.6-4.7, adjusted for pack-years of smoking); however, Beiderbeck-Noll *et al.* (2003: lung cancer, RR=1.3, 95% CI=0.3-5.5, Model 1) found an effect using the basic analysis, but it disappeared in the more extensively controlled analysis (RR=0.8, 95% CI=0.2-3.5, Model 2). Increased risks of lymphatic and hematopoietic cancers were seen in several studies: Pahor *et al.* (1996a: LHC, ICD-9, codes 200-208, RR=2.57, 95% CI=1.13-5.83); Olsen *et al.* (1997a: non-Hodkins lymphoma, ICD-7, codes 200 and 202, SIR=1.4, 95% CI=0.8-2.2); Rosenberg *et al.* (1998: malignant melanoma, ICD version and codes not specified, OR=1.6, 95% CI=0.8-3.0; ≥5 years, OR=1.7, 95% CI not provided, p>0.05).

No animal carcinogenicity studies of verapamil have been reported in the published scientific literature. Two sets of studies in rats – one consisting of administration of verapamil in the diet for two years at doses of 1, 3.5 or 12 times the maximum recommended human daily dose, and the other consisting of administration by an unspecified route of verapamil for 18 months at six times the maximum recommended human daily dose – are briefly summarized in FDA-approved labeling language for verapamil hydrochloride as providing no evidence of a carcinogenic potential (PDR, 2004).

Regarding genotoxicity, one set of studies with human lymphocytes has shown clastogenic effects both *in vitro* and *in vivo*, although studies with other species have not shown such effects. There has been only limited testing of verapamil in standard tests of mutagenicity. Verapamil alone is not mutagenic in *Salmonella* assays. Verapamil has been shown to enhance the effects of certain genotoxic agents in both bacteria and in mammalian cells. On the other hand, in several studies in animals, co-administration of verapamil with known carcinogens has had the effect of reducing tumor incidence.

The mechanism by which verapamil may induce tumors is unknown. While various hypotheses have been suggested (e.g., inhibition of apoptosis; intracellular accumulation of genotoxic agents; direct genotoxicity), there is not a robust dataset supporting any of the hypotheses. Further, the data that do exist provide conflicting results with respect to verapamil's genotoxicity and its ability to suppress apoptosis.

With respect to pharmacokinetics and metabolism of verapamil, factors which may increase exposure to verapamil and/or specific verapamil metabolites include age, gender, genetic predisposition, and concomitant xenobiotic exposures. For example, bioavailability is increased in older (> 60 years) individuals, presumably because of decreased first-pass metabolism. Studies have shown that bioavailability of verapamil is somewhat higher in women; the elimination half-life is longer in women compared to men for both oral and i.v. administration. Information on tissue distribution shortly after verapamil administration from studies in humans, dogs and rats found the highest concentrations in the lung for all three species. Studies in rats indicate that the elimination rate varies across tissues, with elimination in the lungs and kidneys occurring only half as rapidly as in brain, heart and liver.

5.2 Conclusion

Epidemiologic studies of subjects taking verapamil on the whole report an increased overall risk of cancer, although significantly increased risks were found only in a few studies. Overall cancer risk was approximately doubled in the studies that best controlled for potential confounding (Beiderbeck-Noll *et al.*, 2003; Pahor *et al.*, 1996a and 1996b; Jick *et al.*, 1997). Increased risk of LHC with verapamil exposure was seen in the best cohort study (Beiderbeck-Noll *et al.*, 2003). A well-designed breast cancer case-control study (Meier *et al.*, 2000) found increased risks with verapamil exposure, while a case-control study with a more limited design found a strong indication of increased colon cancer risk with verapamil exposure (Hardell *et al.*, 1996). Findings for these cancer sites for verapamil-exposed subjects are consistent with results in some but not all studies which examined site-specific results only for subjects exposed to any CCB (including verapamil). In addition, evidence of a dose-response effect with verapamil exposure was seen for overall cancer risk and exposure duration (as a measure of cumulative exposure) as well as for overall cancer risk and daily dose level in the best, most recently conducted study (Beiderbeck-Noll *et al.*, 2003). The breast cancer case-control study also reported an effect of dose in terms of duration of exposure (Meier *et al.*, 2000).

The mechanism by which verapamil may cause cancer is unknown. One set of studies has shown clastogenic effects of verapamil in human lymphocytes exposed either *in vitro* or *in vivo*. Studies with other species have not demonstrated clastogenic effects following treatment with verapamil. The limited standard testing of verapamil for mutagenicity has shown that verapamil alone is not mutagenic in *Salmonella* assays. Available data from other studies in animals and short-term test systems provide little insight into how verapamil treatment might lead to an increased cancer risk in persons taking it. Results from unpublished long-term bioassays conducted in rats, as described briefly in the PDR (2004), do not provide support for a finding of carcinogenicity. Studies of pharmacokinetics and metabolism of verapamil suggest that specific factors which might increase internal exposure to verapamil and/or specific verapamil metabolites include older age, gender (i.e., being female), and concomitant xenobiotic exposures.

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