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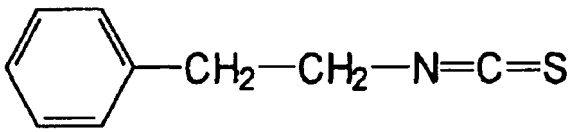
NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN: PHENETHYL ISOTHIOCYANATE

DRUG IDENTIFICATION

CAS Registry No.: 2257-09-2

CAS Name (9CI): (2-Isothiocyanatoethyl)benzene
Synonyms: PEITC
2-Phenylethyl Isothiocyanate
β-Phenylethylisothiocyanate
Phenylethyl Mustard Oil
Molecular Wt.: 163.2
Structure:



EXECUTIVE SUMMARY

Phenethyl isothiocyanate (PEITC) occurs naturally as its thioglucoside conjugate, gluconasturtiin, in many cruciferous vegetables, including watercress [1,2], turnip [3], Chinese cabbage [4], cabbage [5,6], broccoli [5], cauliflower [5], horseradish [4], and canola oil [7]. This glucosinolate undergoes enzymatic hydrolysis by myrosinase whenever the raw wet plant material is crushed, thus releasing PEITC [4].

Chemopreventive effects of PEITC most likely result from its inhibition of specific cytochrome P450 enzymes (*e.g.*, CYP2E) which are able to activate procarcinogens. For example, results from numerous animal efficacy studies have shown that PEITC inhibits lung tumor induction by the tobacco-specific nitrosamine NNK when this drug is administered during the initiation phase of carcinogenesis, but not when administered postinitiation.

PEITC has demonstrated chemopreventive efficacy in several animal models of carcinogenesis when administered prior to carcinogens requiring metabolic activation. These data are sufficient to support clinical development of the agent. In published studies, PEITC inhibited the development of lung adenomas in mice and adenomas and carcinomas in rats treated with NNK and adenomas in mice treated with DMBA. It has also been effective in preventing esophageal squamous papillomas in rats initiated with *N*-methylbenzylnitrosamine (MBN). In addition, PEITC has been shown to inhibit forestomach tumors (type not specified) induced in mice by either DMBA or B(*a*)P. It has also been reported to be effective against hepatocellular adenomas in mice induced by DEN [8] and placental GST-positive liver foci induced in rats with DEN/Glu-P-1 [9]. Thus most of the efficacy of PEITC has been with nitrosamines which are activated by CYP2E. In contrast, it had no chemopreventive effects on DMBA-induced rat mammary tumors or B(*a*)P-induced mouse lung tumors in NCI, Chemoprevention Branch-sponsored testing.

Independent acute and subchronic safety studies have been carried out in Fischer 344 rats and a 14-day

study has been done in female A/J mice. A Chemoprevention Branch-sponsored 90-day toxicity and pharmacokinetics study in dogs has recently been completed. Adverse effects were observed in the GI tract of rats and dogs and in the liver of rats. In the 90-day studies, NOELs were determined to be 40 mg/kg-bw/day (245 μmol/kg-bw/day) for rats and 2 mg/kg-bw/day (12 μmol/kg-bw/day) for dogs.

No clinical trials of PEITC have yet been carried out; however, a Phase I trial sponsored by the Chemoprevention Branch is scheduled to begin in 1996. Selection of an appropriate dose for this Phase I clinical trial will be based on the results of toxicity and efficacy studies in animals and on human consumption in foods. Efficacy of PEITC against NNK-induced lung tumors in Fischer 344 rats was shown at doses around 240 μmol/kg-bw/day for a carcinogen dose of 3.6 μmol/kg-bw/day, a PEITC-to-NNK ratio of ≈67. For smokers (one pack/day) exposed to an estimated 0.5 nmol NNK/kg-bw/day, a PEITC dose of 33 nmol/kg-bw/day (380 μg/day) would provide the same inhibitor-to-carcinogen ratio. In safety studies in rats, a NOEL of about 245 μmol/kg-bw/day has been established. In broadest terms, the efficacious but safe daily dose for a 70-kg human would be in the range of 0.4–2,800 mg; more conservatively, initial daily doses for clinical trials will be about 10 mg (size of the capsule) and up.

Suitable mechanism or drug effect measurements for PEITC might include urinary levels of NAC-PEITC in smoking or non-smoking subjects, the urinary NNK metabolites 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL glucuronide (NNAL-Glu) in smokers, and hemoglobin ester adducts. Inhibition of DNA adduct formation or a decrease in squamous metaplasia/dysplasia in the lung of smokers could provide the basis for intermediate biomarkers for clinical trials.

PEITC may also serve as the lead compound for developing other isothiocyanates as cancer chemopreventive drugs. A series of isothiocyanates was tested for efficacy in the NNK-induced mouse lung tumor assay; the results were correlated to their octanol/water partition coefficients and the observed first-order rate constants for the reaction of isothiocyanates towards glutathione [10]. Results of these experiments indicate that the phenyl ring is not required for chemopreventive efficacy and that secondary isothiocyanates have higher potency than primary. Potency also appears to be correlated to high lipophilicity and low reactivity. If the safety and efficacy of PEITC can be established, more potent isothiocyanates may be developed. The Chemoprevention Branch currently is investigating 6-phenylhexyl isothiocyanate. However, because the phenylhexyl derivative was shown to act as a tumor promoter in rat colon and esophagus, other isothiocyanates will need to be evaluated.

PRECLINICAL EFFICACY STUDIES

PEITC has demonstrated chemopreventive efficacy in several different animal models of carcinogenesis when administered prior to carcinogens requiring metabolic activation. These data are sufficient to support clinical development of the agent. In published studies, PEITC inhibited the development of lung adenomas in mice and adenomas and carcinomas in rats treated with NNK; this effect is most likely the result of its inhibition of cytochrome P450-mediated activation pathways. PEITC also inhibited formation of lung adenomas in mice treated with DMBA. The agent was also effective in preventing esophageal squamous papillomas in rats initiated with MBN. In addition, PEITC has been shown to inhibit DMBA-induced rat mammary tumors (type not specified) and forestomach tumors (type not specified) induced in mice by either DMBA or B(*a*)P. As mentioned above, however, Chemoprevention Branch-sponsored testing in rats has not confirmed its efficacy against DMBA-induced mammary tumors. Furthermore, recent work by Stoner [11] and Moon has not demonstrated any chemopreventive effect of PEITC on B(*a*)P-induced lung adenomas in mice. However, it has also been reported to be effective against hepatocellular adenomas in mice induced by DEN [8] and GST-p-positive liver foci induced in rats with DEN/Glu-P-1 [9].

Most of the preclinical efficacy studies on PEITC completed to date appear in the published literature and were performed independent of the Chemoprevention Branch testing program. The most extensive work has been carried out in the mouse lung adenoma model against the tobacco-specific nitrosamine, NNK. PEITC was effective when administered ig at 5 [12–14] or 25 μmol/day [12,13,15] (*ca.* 0.3 or 1.3 mmol/kg-bw/day) for 4 days prior to carcinogen administration. The agent was also effective when only a single 5 μmol dose was given prior to NNK [16].

PEITC was not effective when given at doses lower than 5 μmol [10,14], when it was administered after NNK (1 or 3 μmol/g diet for 15 wk; *ca.* 0.1 or 0.3 mmol/kg-bw/day) [17], or when B(*a*)P was used as the carcinogen [11,18]. In rats treated with NNK, PEITC significantly reduced the incidence of lung adenomas and carcinomas after 2 years when the agent was administered at 3 μmol/g diet (*ca.* 0.18 mmol/kg-bw/day) for 21 weeks before and during carcinogen administration [13,19]. Thus PEITC appears to be an effective inhibitor when administered during the initiation phase of lung carcinogenesis.

PEITC most likely inhibits NNK tumor induction by inhibiting certain cytochrome P450 enzymes in the lung and thus decreasing formation of reactive intermediates with concomitant inhibition of DNA adduct formation. The major metabolic activation and detoxification pathways of NNK have been studied by Hecht [20,21]. In laboratory animals and humans, NNK is rapidly converted by carbonyl reductase enzymes to the carcinogen NNAL, which is subsequently converted to its diastereomeric glucuronides, NNAL-Glu. These glucuronides are believed to be detoxification products of NNK. Activation of NNK also proceeds by cytochrome P450-mediated α-hydroxylation of the methylene and methyl carbons producing unstable intermediates which spontaneously decompose, forming aldehydes and two electrophilic diazohydroxides. These reactive intermediates form DNA adducts, and one of the diazohydroxides reacts with hemoglobin to form ester adducts. If the α-hydroxylation pathways and other oxidative metabolic pathways of NNK and NNAL are inhibited, the result will be increased excretion of NNAL and NNAL-Glu in urine.

The effect of oral PEITC on the formation of DNA adducts by NNK has been examined. DNA methylation and pyridoxylbutylation in the lung were decreased by PEITC in a dose-dependent manner. Methylation was measured in acid hydrolysates as 7-methylguanine [13,19] or O^6-methylguanine [12,13]. Pyridoxylbutylation was measured as keto alcohol (4-hydroxy-1-(3-pyridyl)-1-butanone; HPB) [19]. PEITC was also shown to inhibit NNK metabolism to HPB and NNAL in mouse lung microsomes [12]. HPB has been measured as a product of the hydrolysis of hemoglobin obtained from smokers or animals treated with NNK [22,23].

When PEITC was administered for 25 weeks to rats at doses of 0.33, 0.4, 0.75, 1.0, 1.5, 2.5, 3.0 or 6.0 μmol/g diet (*ca.* 0.02–0.3 mmol/kg-bw/day), the occurrence of MBN-induced esophageal tumors (primarily squamous papillomas) was significantly reduced in groups receiving ≥0.75 μmol/g diet (≥0.04 mmol/kg-bw/day) [24–27]. In a related study, PEITC was effective in reducing tumor incidence and multiplicity when administered with MBN, but not when given only during the postinitiation stage [28]. The effects of PEITC (10–100 μM) on the metabolism and DNA binding of MBN in cultured explants of rat esophagus have also been examined [24]. PEITC produced a marked dose-dependent inhibition in the binding of MBN metabolites to DNA and in the levels of DNA methylation at the N^7 and O^6 positions of guanine. The agent also reduced the metabolism of MBN by esophageal tissues as indicated by increased amounts of the unmetabolized carcinogen in the culture medium. A similar dose-response inhibition was shown for esophageal DNA methylation when PEITC was fed to rats for two weeks [25].

PEITC showed inhibitory activity against mouse lung and forestomach tumors induced by DMBA when administered in the diet at 5.5 mg/g (*ca.* 2.3 mmol/kg-bw/day) for 4 weeks [29]. The agent was also effective against B(*a*)P-induced forestomach tumors in mice when administered ig as a bolus dose just prior to the carcinogen at 6.7 μmol/dose 3x (*ca.* 0.34 mmol/kg-bw/dose) [18]. It was also effective against rat mammary carcinogenesis induced by DMBA when administered four hours before the carcinogen at a single dose of 55 mg ig (*ca.* 1.1 mmol/kg-bw) [29].

In Chemoprevention Branch-sponsored testing, PEITC significantly inhibited the incidence of NNK-induced lung adenomas and adenocarcinomas in a two-year study in Fischer 344 rats. PEITC was administered at 4 and 8 μmol/g diet (*ca.* 0.24 and 0.48 mmol/kg-bw/day) for 22 weeks, from 1 week before to 1 week after NNK. Tumor inhibition studies in rat mammary glands with the direct-acting carcinogen MNU showed no effect. The drug is currently being tested by the Chemoprevention Branch in the mouse (B(*a*)P) lung model.

The Chemoprevention Branch has also sponsored preclinical tests to evaluate the effects of PEITC on intermediate biomarkers. In one study, the effect of PEITC on oncogene (K-*ras*) and tumor suppressor gene (p53) expression, as well as NNK induction of

precancerous lesions (lung adenomas) was examined in A/J and A/J×TSG-p53 (p53+/+ and p53+/–) F_1 mice [30]. While administration of PEITC before NNK significantly decreased lung adenoma multiplicity in all test groups, it had no effect on the frequency of mutations in the K-*ras* gene in lung tumor DNA. No mutations of the p53 gene were found in any of the tumors analyzed, which suggests that p53 has little, if any, involvement in the development of lung adenomas. Tests in progress evaluating PEITC modulation of biomarkers include PCNA, premalignant lesions, and DNA ploidy in the MBN-induced rat esophagus model, and a rat lung model evaluating cigarette smoke-induced DNA adduct formation.

PRECLINICAL SAFETY STUDIES

Safety: Independent acute and subchronic safety studies have been carried out in Fischer 344 rats, and a 14-day study has been done in female A/J mice. A Chemoprevention Branch-sponsored 90-day toxicity study in dogs was recently completed. Adverse effects in the GI tract of rats and dogs and in the liver of rats were observed. PEITC has shown genotoxic effects *in vitro*, and, as an inhibitor of liver aldehyde dehydrogenase, may have potential to limit the detoxication of carcinogenic aldehydes. The related compound 6-phenylhexyl isothiocyanate has shown tumor promoting activity in the AOM-induced rat colon and MBN-induced rat esophagus models.

In an independent study, the oral LD_{50} for PEITC was estimated to be 862 mg/kg-bw (*ca.* 5.3 mmol/kg-bw) for Fischer 344 rats [781 mg/kg-bw (4.8 mmol/kg-bw) for females and 898 mg/kg-bw (5.5 mmol/kg-bw) for males]. An independent, published 14-day study to determine the maximum tolerated dose (MTD) of PEITC was carried out in female A/J mice [17]. The agent was administered at 0, 1, 3, or 10 μmol/g diet (*ca.* 0, 0.1, 0.4, 1.3 mmol/kg-bw/day). At the highest dose, the only adverse signs were decreased food consumption and body weight gain. Detailed results were not reported.

In an independent 90-day study, PEITC was administered to Fischer 344 rats in NIH-07 diet at concentrations of 0, 500, 1,500, and 2,500 ppm (*ca.* 0, 245, 735, 1,225 μmol/kg-bw/day). At the highest dose, mean body weight was significantly reduced only during the second week of treatment for males and females, although food intake throughout the study was similar in PEITC-treated and control animals. Organ weights were similar in control and treated groups except for the liver. The mean relative liver weight to final body weight and the mean absolute liver weight was significantly greater in male rats from the 1,500 and 2,500 ppm groups. Hematological and biochemical parameters were similar in all groups except for serum alkaline phosphatase, which was significantly reduced in males treated with 2,500 ppm PEITC. There were no treatment-related gross lesions in any rats at necropsy; however, compound-related microscopic changes in the epithelial lining of the forestomach were observed for the 1,500 and 2,500 ppm groups; these changes included increased width of the keratin layer and squamous epithelial cell ghosts retained in the keratin layer. The results of this study indicate that the NOEL for PEITC in Fischer 344 rats is 500 ppm in diet (ca. 245 μmol/kg-bw/day).

A 90-day oral toxicity study in dogs sponsored by the Chemoprevention Branch was recently completed. The study used dose levels of 0, 2, 4, and 8 mg/kg-bw/day (0, 12, 24, 49 μmol/kg-bw/day). Preliminary results reported gastric irritation in all drug-treated groups, while the severity and frequency of diarrhea and vomiting were dose-related. Treatment-related reactive changes were seen in the bladder at the two highest doses, including inflammation, hyperplasia, and hemorrhage. The NOEL was determined to be 2 mg/kg-bw/day (12 μmol/kg-bw/day).

In a recent study [31], the structural analog 6-phenylhexyl isothiocyanate significantly increased the incidence and multiplicity of total intestinal adenocarcinomas in AOM-treated rats when the agent was administered before, during, and after AOM. However, when it was administered only during the initiation stage, no enhancement was seen and tumor multiplicity was significantly reduced. In another study, 6-phenylhexyl isothiocyanate administration before, during and after MBN enhanced formation of papillomas and carcinomas in rat esophagus [32], while PEITC had the opposite effect and inhibited tumorigenesis [27]. In this model, different effects were seen with different carbon chain lengths: C2 and C3 chains inhibited tumor induction, C4 had no effect, and C6 enhanced. Similar differences by structure may be true for the AOM-induced rat colon model.

PEITC has been shown to induce chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells at concentrations of 0.9–1.2 μg/ml [33]. In a recent study, PEITC was shown to

be a potent inhibitor of hepatic aldehyde dehydrogenase in rats [34]. The authors suggest that since many procarcinogens are activated to carcinogenic aldehydes, PEITC might prevent their detoxication and thus enhance their carcinogenic action.

ADME: The distribution and metabolism of PEITC has been investigated in A/J mice [35]. Mice were administered 5 μmol [^{14}C]PEITC by gavage and sacrificed at 1, 2, 4, 8, 24, 48, or 72 hours after dosing. Radioactivity present in the spleen, heart, liver, lung, kidney, brain, urine, and feces was measured. Lung showed maximum radioactivity between 4 and 8 hours after dosing. Approximately 50% of the radioactivity was excreted in the 48 hour-urine and 19% in the feces. More than 80% of the urinary metabolites were PEITC conjugates derived from glutathione conjugation. Two major urinary metabolites identified were the N-acetylcysteine (NAC) conjugate of PEITC and a cyclic mercaptopyruvate conjugate, which accounted for approximately 25% and 10%, respectively, of the PEITC administered.

PEITC is known to be unstable at acid pH (such as that found in the stomach). When rats were administered PEITC orally, it was rapidly converted to phenethylamine. When humans consumed watercress, which contains significant levels of PEITC in the form of a thioglucoside, dose-dependent urinary excretion of the NAC-PEITC conjugate was observed. NAC-PEITC may be specific to food material.

CLINICAL SAFETY: PHASE I STUDIES

A Chemoprevention Branch-sponsored Phase I multidose safety and pharmacokinetics clinical trial of PEITC in chronic smokers will begin in 1996 (Dr. Ronald H. Blum, NYU Kaplan Comprehensive Cancer Center).

Drug Effect Measurement: Dose-dependent urinary excretion of the NAC-PEITC conjugate has been observed following ingestion of watercress, which contains high levels of the PEITC glucosinolate [2]. Measurement of this urinary conjugate may be suitable as a drug effect measurement. In addition, NNAL and NNAL-Glu urinary concentrations are increased dose-dependently by administration of PEITC in NNK-treated rats (see Drug Effect Measurement Issues, below). Measurement of these metabolites may also be suitable drug effect measures in smokers.

Safety: No toxicity was observed in four subjects consuming single doses of 30 and 57 g watercress [ca. 7.6 and 15 mg PEITC (ca. 0.7 and 1.3 μmol/kg-bw), respectively] [2]. The latter is about 40x the dose estimated to be effective in human smokers based on chronic rat data.

ADME: The metabolites of PEITC were quantified in the urine of humans who had consumed watercress [2]. Dose-dependent urinary excretion of the NAC-PEITC conjugate was observed. In general, the peak of excretion was observed 2–4 hours after ingestion. NAC-PEITC was completely excreted within 24 hours of ingestion. PEITC is known to be unstable at acid pH (such as that found in the stomach). When rats were administered PEITC orally, it was rapidly converted to phenethylamine.

CLINICAL EFFICACY: PHASE II/III STUDIES

No Phase II or III clinical studies have been conducted by the NCI, Chemoprevention Branch or others. If the Phase I study is successful, then Phase II trials in lung and esophagus will be considered.

PHARMACODYNAMICS

Efficacy studies in rats showed that a PEITC dose of 240 μmol/kg-bw/day was effective against an NNK dose of 3.6 μmol/kg-bw/day; this is a PEITC to NNK ratio of ≈67. In smokers, the daily dose of NNK is ≈0.5 nmol/kg [36], and the corresponding human dose of PEITC to achieve the same ratio is 33 nmol/kg-bw/day (380 μg); this is several thousand times less than the PEITC dose administered to rats. In rats, safety studies established a NOEL of 40 mg/kg-bw/day (245 μmol/kg-bw/day). In broadest terms, the efficacious but safe daily dose for a 70-kg human would be in the range of 0.4–2,800 mg; more conservatively, initial daily doses for clinical trials will be about 10 mg.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

Urinary levels of NAC-PEITC in smoking or nonsmoking subjects, urinary NNAL and NNAL-Glu in smokers, and hemoglobin ester adducts may be suitable mechanism or drug effect measurements for PEITC. This should be verified during the Phase I trial.

PEITC has been shown to specifically inhibit pulmonary cytochrome P450 enzymes involved in the activation of NNK [37,38]. Therefore, it is expected

activation of NNK [37,38]. Therefore, it is expected that rats or humans treated with NNK and PEITC will show a decrease in hemoglobin adducts and an increase in excretion of NNAL and NNAL-Glu. The latter two products would increase because the competing metabolic activation pathways had been blocked. Studies have shown a significant 4–8 fold increase in total urinary NNAL plus NNAL-Glu in rats treated with isothiocyanates compared to those treated with NNK alone. Recently, an increase in NNAL plus NNAL-Glu in the urine of smokers consuming specified amounts of watercress (containing *ca.* 19–38 mg PEITC/day) was observed [39]. The percent increase of the urinary metabolites correlated to the intake of PEITC. Urinary levels of NNAL and NNAL-Glu returned to near baseline in the follow-up period. Thus, measurement of the ratio of NNAL to NNAL-Glu in urine or release of HPB from hemoglobin adducts in blood could serve as noninvasive drug effect measures of PEITC and its effect on NNK metabolism in clinical trials with smokers. The potential application of these measurements in clinical studies has been reviewed by Hecht *et al.* [40,41].

Safety Issues

It will be important to select a dose of PEITC for clinical trials with smokers that is both safe and effective in inhibiting metabolic activation of NNK. If safe and effective doses in humans are similar to those in rats and dogs, a wide range of safe doses should be available for establishing the dose-response relationships for PEITC inhibition of NNK metabolism. Conservatively, initial daily doses for clinical trials will be about 10 mg and up. PEITC is a known enzyme inducer and effects on liver were observed in rats; safety monitoring in clinical trials should include enzyme measures of liver function. Adverse effects on the GI tract have been observed in rats and dogs, so these should also be closely monitored. The potential of PEITC as a tumor promoter should also be investigated.

Pharmacodynamics Issues

Pharmacokinetic studies will be important for determining the number of daily doses needed to achieve and maintain steady state PEITC levels in plasma during hours when smoking occurs.

Regulatory Issues

American Health Foundation (AHF) holds two utility patents covering the synthesis and use of arylalkyl isothiocyanates [42,43]. These patents cover the use of this class of chemicals for inhibiting the formation of lung tumors in mammals. In addition, they cover a method for synthesizing selected long chain isothiocyanates. This may indicate that an agreement between Chemoprevention Branch and AHF will be needed to pursue Phase II studies of PEITC or development of the long chain analogs.

Intermediate Biomarker Issues

One of the diazohydroxides formed during metabolic activation of NNK methylates DNA in NNK target tissues, producing mutations, mainly of the G→A type. The other diazohydroxide alkylates DNA, producing both G→A and G→T mutations. Hydrolysis of DNA obtained from animals treated with NNK or from smokers produces HPB, which is a biomarker of the metabolic activation of NNK [22, 23]. Smokers' urine contains quantifiable amounts of NNAL and NNAL-Glu as biomarkers; the ratio of NNAL-Glu to NNAL may be useful as an index of NNK detoxification and decreased risk [36].

PEITC has demonstrated its ability to decrease premalignant lesions in animal studies, such as adenomas in mouse and rat lung. A decrease in squamous metaplasia/dysplasia in lung could be assessed as an intermediate marker in a Phase II trial of PEITC in smokers.

Supply and Formulation Issues

PEITC is available from a number of chemical suppliers. For preclinical testing it has generally been obtained from Aldrich Chemical Company. RP Scherer, under an agreement with AHF, is preparing 9.4 mg PEITC softgel capsules to be used in clinical trials. Placebo will also be provided. Inert ingredients include glycerin, gelatin, titanium dioxide, corn oil, and plurol oleique. A letter has been sent to the FDA to allow AHF to reference Scherer's Drug Master File. The suitability of this product is being investigated. Pills will be bottled and stability testing will be performed.

Clinical Studies Issues

Toxicity testing in dogs may need to be completed and results summarized before clinical trials can be initiated. Results of a single-dose Phase I trial should be obtained before a multidose study is initiated. If a safe dose is defined in a Phase I study, then a Phase

II trial in smokers would be considered based on pharmacokinetics and animal efficacy results. Similarly, a Phase II trial in the esophagus will be considered. PEITC appears to have specific application as an antiinitiator in situations where the presumed carcinogen requires metabolic activation, as in the case of smokers. A Phase II trial with oral leukoplakia as the target in smokeless tobacco users might also be considered.

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Table I. Clinical Trials of Phenethyl Isothiocyanate Sponsored/Funded by NCI, DCPC

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Dose(s) Treatment Duration	Endpoint(s)	Remarks
Phase I (Safety and ADME)					
NO1-CN-55120 Phase I Safety and Pharmacokinetic Clinical Trials of Phenethyl Isothiocyanate in Chronic Smokers (Dr. Ronald H. Blum, MD, NYU Kaplan Comprehensive Cancer Center) 6/95–	---	Asymptomatic smokers with urinary cotinine levels >100 ng/ml ≈25 subjects (5/dose)	Single dose: 0, 10, 20, 30, or 40 mg	Safety, pharmacokinetics, effect on NNK metabolism	Study to start in 1996
Phase II (Dose-titration, efficacy, intermediate biomarkers)					
Phase II Efficacy Trial in Chronic Smokers	Lung	Asymptomatic smokers with urinary cotinine levels >100 ng/ml	---	---	Under consideration

PHENETHYL ISOTHIOCYANATE DEVELOPMENT STATUS