CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

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NDA #21-330

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SPONSOR: SmithKline Beecham Consumer Healthcare, L.P.
Parsippany, NJ

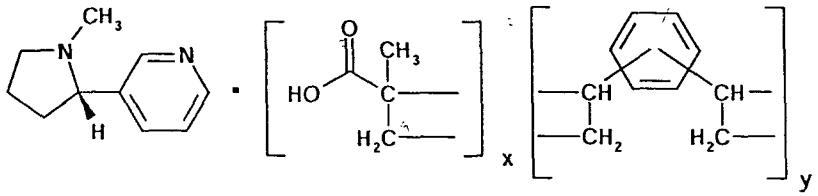
DRUG:

Trade Name: Nicotine Polacrilex Lozenges, 2 mg and 4 mg

Chemical Name: 2-propenoic acid, 2-methyl-polymer with diethenylbenzene, complex with (S)-3-(1-methyl-2-pyrrolidinyl) pyridine; Methacrylic acid polymer with divinylbenzene, complex with nicotine

CAS Registry Number: 96055-45-7

Structure (from Sponsor):



Empirical formula: $C_{10}H_{14}N_2(C_4H_6O_2)_x(C_{10}H_{10})_y$

Relative molecular mass: [redacted]

where: x = number of [redacted] units per NPA molecule
y = number of [redacted] units per NPA molecule

RELATED INDs/NDAs/DMFs: IND 56,295; DMF [redacted] DMF [redacted]

PHARMACOLOGIC CLASS: Nicotinic cholinergic receptor agonist

PROPOSED CLINICAL INDICATION: Reduction of withdrawal symptoms, including nicotine craving associated with quitting smoking

FORMULATION (Sponsor's Table):

Table 4.A.2.b-1
Quantitative Composition of Nicotine Polacrilex Lozenges

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
Nicotine Polacrilex, USP[1]		
Mannitol, USP[2]		
Sodium Alginate, NF[2]		
Xanthan Gum, NF[2]		
Potassium Bicarbonate, USP[2]		
Calcium Polycarbophil, USP[2]		
Sodium Carbonate, NF[2]		
Aspartame, NF		
Magnesium Stearate NF		
Total lozenge weight	1200.000	1200.000

[1] Amount of Nicotine Polacrilex, USP will vary depending upon the potency (nominally x nicotine).

[2] Amount of these ingredients (added as is adjusted dependent on the calculated quantity of Nicotine Polacrilex, USP used.

[3] Used as a and evaporates during the

ROUTE OF ADMINISTRATION: Oral

PREVIOUS HUMAN EXPERIENCE: These is extensive human experience with nicotine polacrilex from the use of the marketed Nicorette® gum.

RATIONALE: Nicotine dependence maintains tobacco use and makes it difficult to abstain. This was the premise for developing nicotine replacement products for smoking cessation therapy. If a smoker is switched to another source of nicotine, this would prevent the withdrawal symptoms while the person could adapt to being without the tobacco product. The person could then be weaned off tobacco. Also, pure nicotine does not contain any of the tars and other toxins found in tobacco products when smoked or unsmoked.

BACKGROUND: [Note: In this NDA, the sponsor is requesting a direct-to-OTC switch.]

No animal studies have been conducted with the Nicotine Polacrilex Lozenge. However, the active ingredient, nicotine polacrilex, has been studied under IND #17,689 (Nicotine Polacrilex Gum), NDA #18-612 (2 mg Nicotine Polacrilex Gum), and NDA #20-666 (4 mg Nicotine Polacrilex Gum).

The basic pharmacology and toxicology of nicotine was reviewed by the sponsor from published literature reports. The following summary of nicotine was taken essentially from the sponsor's summary with some revisions and additional studies included by this reviewer.

PHARMACOLOGY AND TOXICOLOGY OF NICOTINE:

Pharmacodynamics:

Nicotine, 1-methyl-2-(3 pyridyl) pyrrolidine, is the chief alkaloid in tobacco products which binds stereoselectively to acetylcholine receptors at the autonomic ganglia of the adrenal medulla, at the neuromuscular junctions, and in the brain (1). The pharmacology of nicotine is complex and includes a variety of autonomic effects, both adrenergic and cholinergic.

The pharmacological effects of nicotine are generally dose related. Low doses of nicotine cause ganglionic stimulation and high doses cause ganglionic blockade following brief stimulation. At low doses, such as those associated with smoking cigarettes, nicotine's cardiovascular effects, including increases in heart rate and blood pressure, appear to be mediated by the central nervous system through activation of chemoreceptors, afferent pathways or by a direct effect on the brain stem. The result is sympathetic neural discharge of adrenaline resulting in an increase in blood pressure and heart rate (1).

At high doses, nicotine is thought to act directly on the peripheral nervous system, producing ganglionic stimulation and the release of adrenal catecholamines with resultant hypotension and bradycardia. This effect has been demonstrated in rats when nicotine was orally administered in the drinking water for 12 weeks at doses of 1.14, 2.28, 3.42 or 4.56 mg/kg/day, resulting in a biphasic pressor-depressor response at the two lower doses, and only a depressor response at the higher doses (2). In general, the cardiovascular responses are due to stimulation of ganglia and the adrenal medulla together with discharge of catecholamines from sympathetic nerve endings (1).

Nicotine's cardiovascular effects include increased heart rate, systemic arterial pressure, cardiac output, stroke volume and myocardial contractility. These effects result in increased myocardial oxygen demand (3,4).

Nicotine markedly stimulates the central nervous system. Most of the central nervous system effects of nicotine are due to its direct action on specific brain receptors, leading to the release of acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine, vasopressin, growth hormone and adrenocorticotrophic hormone (ACTH). Changes in secretion of glucocorticoids and several anterior and posterior pituitary hormones have been reported (1,3,5).

Nicotine increases oxygen consumption, basal metabolic rate, blood sugar and lipids. It causes hyperglycemia in fasted rabbits and dogs. Animal studies also support the view that nicotine is an enzyme inducer in the liver (3). Nicotine has been reported to be harmful to the gastric mucosa because it increases acid and pepsin secretions, gastric motility, gastric reflux of bile salts, the risk of *Helicobacter pylori* infection, platelet-activating factor and vasopressin secretion (6).

Nausea and vomiting are the most common symptoms of acute nicotine poisoning in man. In animals, vomiting and diarrhea have been observed. The responses are caused by both central and peripheral actions of nicotine. Excessive doses of nicotine produce tremors followed by convulsions. Lethal doses of nicotine cause peripheral curare-like paralysis of the respiratory muscles. Similarly, nicotine-induced bradycardia is of reflex origin. Thus, extremely high doses of nicotine (overdose) cause transient stimulation followed by depression and paralysis of the central nervous system, affect peripheral autonomic nervous system ganglia and nerve endings on

skeletal muscles. Death may occur within a few minutes and is most often due to paralysis of the respiratory muscles (1).

Many individuals and animals develop tolerance to drugs after taking repeated doses, namely a given dose produces less effect or increasing doses are required to achieve a specified intensity of response. It has been suggested that tolerance is due to altered sensitivity to drugs. Studies in mice and rats of various strains indicate differences in sensitivities to nicotine are due to differences in nicotine receptors in the brain. It has been determined that tolerance to nicotine in rats can develop quickly, may be measured easily and persists for prolonged periods after withdrawal. Partial tolerance has been reported for some of the cardiovascular effects of nicotine, as well (7).

Pharmacokinetics:

Absorption:

Nicotine is rapidly absorbed across alveolar, oral and gastrointestinal membranes (5). The absorption of nicotine through the alveoli of the lung appears to be related simply to the concentration of alkaloid, whereas buccal, gastrointestinal and bladder absorption is influenced by pH. Specifically, absorption is greater at a higher pH, as a higher proportion of nicotine is not ionized (8).

Distribution:

In the rat, nicotine exhibits a rapid biexponential decline in plasma with an apparent elimination half life of about 1 hour and a large volume of distribution. Cotinine, the major metabolite of nicotine, appears rapidly in the plasma following nicotine administration and has a slower monophasic elimination with an apparent half life, of about 6 hours. Other metabolites, in addition to cotinine, are also formed very rapidly and decline biexponentionally with apparent half lives of approximately 23 hours, indicating that while nicotine is rapidly eliminated, its metabolites persist in the plasma for far longer. The pharmacokinetics of nicotine are not dose dependent in the rat (9,10).

Metabolism:

Nicotine is primarily metabolized by the liver in humans, rabbits, guinea-pigs and rats to cotinine, the major metabolite, and nicotine N-oxide. Both compounds are formed by two independent oxidative pathways and are precursors for other metabolic products. In humans primarily CYP2A6 and/or CYP2B6 have been associated with nicotine metabolism to cotinine, while only a minor contribution is attributed to CYP2D6 (11,12). As many as 18 urinary metabolites have been described (13).

The predominant metabolic pathway for nicotine varies with animal species (8,14). N-methylation is an example of species variability. The rat does not N-methylate nicotine, the guinea-pig only N-methylates R(+) nicotine, and the dog and man N-methylate both enantiomers (15).

Guinea-pigs metabolize nicotine to cotinine and nicotine N-oxide but the N-oxidation is the principal metabolic route in this species (16,17). Additional investigations have shown that guinea-pigs selectively metabolize R(+) nicotine but not S(-) via N-methyl transferase to N-methylnicotinium-ion (18,19). Other urinary metabolites detected in guinea-pigs are 3-hydroxycotinine and nornicotinine [only with R(+)]. Data obtained with continuous subcutaneous infusion of nicotine to guinea-pigs over 23 days indicate that nicotine probably does not induce the hepatic enzymes responsible for its own metabolism (20).

In rabbits the cotinine formation pathway predominates (16). *In vitro* evaluations with rabbit liver confirmed that cotinine is derived from the aldehyde oxidase-catalysed oxidation of S(-) nicotine delta-1, 5-iminium ion, the principal two electron oxidation product of S(-) nicotine (21). In rodent lung and liver tissues lacking aldehyde oxidase, the iminium intermediate is oxidized by monoamine oxidase B to nicotyrine, which may undergo further processing to 5-hydroxy pyrrolinone (22).

Nicotine N-oxide is a tertiary amine N-oxide, a class of compounds generally regarded as non toxic. Its formation is catalyzed by flavin-containing monooxygenase. Nicotine N-oxide can be reduced back to nicotine by gut flora under anaerobic conditions and may serve as a reservoir for nicotine in the body (23,24).

Excretion:

The kidney is the main excretory pathway of nicotine and its metabolites. Less than 20% of absorbed nicotine is excreted unchanged in the urine. Nicotine is excreted by glomular filtration and tubular secretion. Excretion is influenced by pH and urinary output (10,25). Nicotine N-oxide is excreted virtually unchanged after intravenous administration to man (13). In the urine of tobacco users, nicotine, cotinine and trans-3'-hydroxycotinine and their glucuronides together with the N-oxides of nicotine and cotinine, account for more than 90% of the ingested dose of nicotine.

Toxicology:

Single Dose Toxicity:

The toxicity of single doses of nicotine has been extensively studied and reported in the literature. Results of acute toxicity studies in several animal species using various routes of administration indicate that nicotine is relatively toxic, with reported LD_{50} values generally less than 100 mg/kg (26-33). Oral administration of nicotine to mice has been reported to result in an LD_{50} value of 24 mg/kg, while the oral LD_{50} reported for rats was approximately 188 mg/kg (26,28). Additionally, oral doses of 10 to 12 mg/kg have been reported to be lethal in dogs (28). Lethal doses of nicotine cause peripheral curare-like paralysis of the respiratory muscles. Extremely high doses of nicotine (overdose) cause transient stimulation followed by depression and paralysis of the central nervous system. Such doses also affect peripheral autonomic nervous system ganglia and nerve endings on skeletal muscles. Death usually occurs within a short period of time and is most often due to paralysis of the respiratory muscles (1).

Oral doses of nicotine that have been reported to be lethal in animals are approximately 8- to 150-fold greater than nicotine exposures that would result from use of Nicotine Polacrilex

Lozenges. Additionally, the toxicologic profile of nicotine in animals has been largely superseded by the extensive human experience with this agent. Based on the established clinical experience with similar nicotine replacement therapy products, acute toxic reactions would not be anticipated from use of Nicotine Polacrilex Lozenges at the recommended dosage.

Repeat Dose Toxicity:

Subacute and chronic exposure to nicotine has been shown to result in complex and varied toxic effects in animals, which are generally related to an exaggeration of its pharmacological activity. The major effects observed following subacute and chronic dosing of nicotine to mice, rats, rabbits, and dogs consist of cardiovascular and metabolic effects. Cardiovascular effects of nicotine include biphasic pressor-depressor responses at low doses and only depressor responses at high doses. This effect was demonstrated in rats when nicotine was orally administered in the drinking water for 12 weeks at doses ranging from 1.14 to 4.56 mg/kg/day, resulting in a biphasic pressor-depressor response at lower doses, and only a depressor response at higher doses (2). Additionally, elevated peripheral resistance has been shown to be another cardiovascular effect of nicotine. This effect was demonstrated in dogs when nicotine was administered intramuscularly for 2 years at a dosage of 840 mcg/kg/day (34).

Metabolic effects of nicotine consist of decrease in body fat, increased pancreatic biosynthesis and accumulation of digestive enzymes in the pancreas, and increased adrenal weights. These effects have been demonstrated in mice subcutaneously administered 1 mg/kg nicotine five times daily, six days weekly for 6 weeks, and in rats administered 5, 15, or 50 mg nicotine (3 week release pellets) by subcutaneous implant for 12 weeks (35, 36).

In addition, subcutaneous administration of nicotine to female rats for 3 months at doses of 3.0 or 4.5 mg/kg/day have been shown to result in significantly lower serum levels of 25-hydroxyvitamin D at both dose levels, and adverse effects on bone formation at the high dose level (37).

Reproductive Toxicity:

Adverse reproductive effects of nicotine have been reported, and consist of effects on pregnancy, effects on fetal development, teratogenic effects, and effects on fertility. These effects have been shown to be dependent on dose, duration of treatment, and route of administration. In general, most effects on the fetus have been shown to be associated with maternal toxicity. Effects of nicotine on pregnancy have been shown to include decreased maternal weight gain during pregnancy, increased uterine vascular resistance, altered patterns of luteinizing hormone and prolactin release, increased fetal resorptions, and decreased litter size. These effects have been demonstrated in mice, rats and sheep by various routes of administration. When administered to mice at a dosage of 25 mg/kg subcutaneously as a single dose, or 6 mg/kg intraperitoneally as repeated doses on two or three consecutive days between days 5 and 15 of gestation, nicotine resulted in an increase in the number of fetal resorptions and a decrease in litter sizes (38). These effects were also observed in rats that were administered doses up to 5.0 mg/kg nicotine by subcutaneous injection, twice daily throughout pregnancy (39,40). Increased uterine vascular resistance has been demonstrated in sheep that were administered nicotine by intravenous infusion at a rate of 14 to 32 mcg/minute on days 97 through 117 of gestation, or by

intramuscular injection at a dosage of 10 mg/day, 5 days per week on days 60 through 125 of gestation (41,42). An altered developmental profile of luteinizing hormone has been demonstrated in rats receiving nicotine at doses up to 4.5 mg/kg/day administered orally via drinking water during gestation, lactation, or a period ranging from one week prior to conception throughout lactation (43-45). Additionally, lower maternal prolactin levels and milk reduction, as well as decreased birth weights and increased fetal mortality have been observed in rats that were administered 0.5 or 1.0 mg nicotine, twice daily from day 5 of gestation throughout pregnancy (45,46).

Effects of nicotine on fetal development have been shown to include decreased fetal weight, pup weight, and pup survival, and changes and delays in postnatal central nervous system development. When administered subcutaneously to mice at doses up to 2.7 mg/kg/day during days 1 through 6 of gestation, or during gestation days 1 through 6, 7 through 13, or 13 through termination of pregnancy, nicotine resulted in an increased incidence of stillbirths and neonatal deaths, decreased gestation period, and delays in postnatal development (45,47,48). Infusion of nicotine to rats via osmotic pump at doses of 4.5 or 9.0 mg/kg/day on days 6 through 12 of gestation was also shown to result in decreased fetal weight and delayed fetal development (49). Subcutaneous administration of 3.5 mg/kg/day nicotine alone or in combination with 1.7 mg/kg/day mecamylamine to female CD rats on days 6 through 15 of gestation, or to female New Zealand White rabbits on days 6 through 18 of gestation resulted in lower fetal weights and retarded ossification only in rats (50).

Decreased pup weight, altered profile of pup brain DNA and RNA, and altered development profile of ornithine decarboxylase (enzyme marker related to cellular maturation) has been demonstrated in rats that were administered nicotine by infusion via mini osmotic pump at a dosage approximating 6 mg/kg/day on days 4 through 20 of gestation (44,45,51). These effects occurred at doses that were not maternally toxic, and were attributed to premature activation of specific neurotransmitter receptors in the fetal brain, eliciting abnormalities of cell proliferation and differentiation; effects that may potentially be manifested as cognitive and learning defects during childhood and adolescence (98).

Subcutaneous administration of nicotine to female Wistar rats at a dosage of 1 mg/kg/day from day 1 of gestation through post-natal day 21 resulted in developmental effects in the lungs of offspring, consisting of lower lung volumes, smaller internal surface area of the lungs, and severely suppressed lung alveolarisation (52).

Teratogenic effects of nicotine have been reported in mice, and consist of skeletal defects predominantly of the digits and joints, but also spinal curvature and cleft palate. These effects were observed when mice were administered 25 mg/kg nicotine subcutaneously as a single dose, or 6 mg/kg intraperitoneally as repeated doses on two or three consecutive days between days 5 and 15 of gestation (38).

Effects on neurotransmitter receptor expression and behavior have also been demonstrated in offspring exposed to nicotine pre- and/or postnatally. Subcutaneous administration of nicotine to female rats at a dosage of 0.75, 1.5 or 3.0 mg/kg/day via implanted osmotic minipumps from day 4 of gestation through postnatal day 16 resulted in transient hyperactivity of offspring. Evaluation of locomotor activity in nictotine-exposed pups on postnatal day 14 revealed quantitative differences in hyperactivity. Pups exposed to the low dose of nicotine exhibited less of an increase in locomotor activity than pups exposed to the highest dose of nicotine. In contrast, pups exposed to 1.5 mg/kg/day nicotine did not exhibit significant

signs of hyperactivity, which may be attributable to a biphasic effect. Evaluation of locomotor activity on postnatal day 21 revealed a lack of hyperactivity in all nicotine-exposed pups, most probably due to a down regulation of nicotinic receptor sites (53). Subcutaneous administration of 66 mcg/kg nicotine for 5 consecutive days to neonatal male mice, aged 3, 10, or 19 days resulted in hypoactivity upon challenge with subcutaneous doses of nicotine (40 and 80 mcg/kg) at 4 months, only in mice exposed to nicotine on postnatal days 10 through 14. The response of saline controls and the other neonatal age categories to nicotine at 4 months of age was an increase in activity. Evaluation of spontaneous behavior at 4 months revealed no differences between animals exposed to saline or nicotine neonatally. At no time during the neonatal period could low-affinity nicotine-binding sites be found following nicotine treatment, but the persistence of this effect was evident only in adult mice exposed to nicotine on postnatal days 10 through 14 (54).

Pre- and postnatal exposure to nicotine has also been shown to affect processes relating to autonomic response to hypoxia. Subcutaneous administration of nicotine bitartrate (approximately 2 or 6 mg/kg/day nicotine base) to female rats on days 4 through 21 of gestation, followed by subcutaneous injection of nicotine bitartrate (approximately 0.3 of 3.0 mg/kg nicotine base) to offspring on postnatal days 1 to 4, 11 to 14, or 21 to 24 resulted in the enhancement of cardiac M2-muscarinic cholinergic receptors in nicotine-exposed pups. Coincidentally, stimulatory beta-adrenergic receptors were decreased in these animals. Studies of adenylyl cyclase activity confirmed that the changes in receptor binding represented functional alterations: the stimulatory response to isoproternol was reduced by prenatal nicotine exposure, whereas the inhibitory response to carbachol was enhanced. Elevations of M2-muscarinic receptor binding were not generalized to all tissues, as the same prenatal nicotine exposure elicited a reduction in these receptors in the brainstem. Prenatal nicotine exposure had no effect on brainstem M1-receptor binding. Postnatal administration of nicotine produced similar brainstem receptor effects when treatment was conducted during the first postnatal week, but not thereafter. Postnatal nicotine exposure did not affect cardiac M2-receptor binding. Thus, during a critical developmental period, nicotine exposure produces cardiac and brainstem receptor imbalances that favor inhibitory responses, effects that can contribute to morbidity and mortality evoked by hypoxic episodes (55). Subcutaneous administration of 6 mg/kg/day nicotine to female Sprague-Dawley rats from day 6 of gestation to days 5 or 6 postpartum did not alter the gasping, heart rate pattern, or the time to last gasp of nicotine-exposed pups during a single hypoxic exposure. However, perinatal exposure to nicotine followed by repeated exposures to hypoxia resulted in autoresuscitation failure that was associated with cardiac arrhythmia that preceded cessation of gasping in normal animals. Pups from dams treated with only vehicle were able to autoresuscitate from 18 periods of hypoxia, whereas pups exposed perinatally to nicotine were able to resuscitate from only 12 periods of hypoxia. These findings provide evidence that perinatal exposure to nicotine impairs the ability of newborn rats to autoresuscitate from primary apnea during repeated exposures to hypoxia (56).

Effects of nicotine on female fertility have been evaluated in rats and mice. Nonpregnant female rats receiving 6.25 mg/kg nicotine 2, 3, or 4 times on a single day exhibited a decrease in the number of oocytes in the fallopian tubes, and a decrease in the concentration of serum estradiol (57). Oral or intraperitoneal administration of nicotine to female mice at a dosage of 3 mg/kg/day for 15 days, beginning during the estrus phase of the cycle, resulted in a number of changes to the ovary and uterus (58). Oral administration of nicotine was less effective than

intraperitoneal administration of nicotine in the induction of the observed effects. This may be due to the fact that the intraperitoneal route facilitates the rapid absorption of nicotine, while oral administration of nicotine is subjected to the first-pass effect in the liver, where it undergoes biotransformation through hepatic microsomal enzyme-drug metabolizing systems and becomes less potent. In contrast, administration of 7.5 IU pregnant mare serum and either 0, 5.0, 7.5 or 10.0 mg/kg nicotine at 3 hours before and 3 hours after injection of 5 IU human chorionic gonadotropin to female mice resulted in no significant effects on oocyte meiotic maturation (59).

Effects of nicotine on male fertility have been evaluated in rats. Male rats receiving nicotine intraperitoneally at a dosage of 1.26 mg/kg/day for 1, 2, 4, or 8 weeks exhibited a decrease in testis weight, and a reversible decrease in Sertoli cell numbers with impairment of spermatogenesis (60). Oral or intraperitoneal administration of nicotine to male Wistar rats at a dosage of 4 mg/kg/day for 30 days was reported to result in a variety of changes in the epididymis and vas deferens. Intraperitoneal administration of nicotine resulted in significant changes in almost all of the parameters evaluated, while oral administration of nicotine resulted in changes that were non-significantly different from the controls in almost all of the parameters evaluated (61)

Mutagenicity:

The mutagenic potential of nicotine and its metabolites, particularly cotinine, has been reported in the literature using a variety of assays. Nicotine and four of its metabolites, cotinine, cotinine N-oxide, nicotine N-oxide and trans-3'-hydroxycotinine, have proved negative when tested for mutagenicity with various strains of *Salmonella typhimurium*, with and without metabolic activation (62,63,64). In contrast, in the *Escherichia coli* [pol A + /A -] test nicotine induced repairable DNA damage, whereas cotinine and nicotine N-oxide did not (62). Similarly in *in vitro* studies with *Saccharomyces cerevisiae* yeast cells, nicotine was found to be mutagenic at 100 ppm (65).

While an induction of chromosomal aberrations in Chinese Hamster Ovary cells has been noted in the presence of nicotine, only when chromosomal and chromatid gaps were incorporated into the statistical analysis, contradictory results have been reported for Sister Chromatid Exchange rate (66,67,68). More recently, nicotine, cotinine, cotinine N-oxide, nicotine N-oxide and trans-3'-hydroxycotinine at doses up to 1000 mcg/ml did not increase the frequency of Sister Chromatid Exchange rate in Chinese Hamster Ovary cells (64).

Nicotine was found to be cytotoxic in an *in vitro* assay with human leukocytes (0-2.0 mcg/ml). *In vivo* doses of 0.07-0.09 mcg nicotine/mouse resulted in chromosomal aberrations characterized by aneuploid cells and translocations. Surprisingly however, no other forms of structural abnormalities such as chromosomal breakage, expected alongside translocations, were observed (69).

Carcinogenicity:

The carcinogenic potential of tobacco smoke and its constituents including nicotine, smoke condensate and tobacco specific nitrosamines has been extensively studied and reported in the literature. The literature suggests that neither nicotine nor its primary metabolites, cotinine and nicotine N-oxide, are carcinogenic (70-74). In contrast, tobacco smoke contains a variety of

different classes of carcinogens such as nitrosamines and polycyclic aromatic hydrocarbons (75, 76).

Nicotine has been evaluated in a variety of animal models for its carcinogenic potential. The majority of evidence indicates that nicotine itself is not carcinogenic (70-72, 74), although in an early investigation (77) daily administration of high doses of nicotine subcutaneously for approximately 6 months to rats produced hyperplasia of the noradrenaline containing cells in the adrenal medulla. This effect results from exaggeration of a pharmacological effect of nicotine in the adrenal medulla. In another study, it was suggested that cotinine may cause lymphoreticular sarcoma of the large intestine in rats (78), but this study could not be replicated (73). In all other studies no carcinogenic effect was observed.

Nicotine and its metabolite nicotine N-oxide have shown some cocarcinogenic potential in a number of studies reported in the literature. Several well-established models of chemically induced carcinogenesis have been used to detect nicotine-related changes in tumor expression. Nicotine at concentrations of 2.5 or 5.0 mg/ml significantly enhanced the carcinogenic activity of a topically applied solution containing benzo-a-pyrene (BaP) and 12-0-tetradecanoylphorbol-13-acetate (TPA) when administered to mice, and no difference in effect was detected between the two doses. In the same model a 6 mg/ml dose of nicotine caused early inhibition of carcinogenesis, indicating that the optimum nicotine concentration for a cocarcinogenic effect lies between 2.5 and 5.0 mg/ml. There was no significant difference between the control and cotinine (2.5 or 10 mg/ml) groups, suggesting that metabolic conversion of nicotine to cotinine did not account for the cocarcinogenic activity of nicotine. Mice treated with solutions of nicotine N-oxide at doses of 2.5 or 10 mg/ml developed half as many tumors as did the controls, particularly during the first 30 weeks of the study. Therefore, metabolism of nicotine to nicotine N-oxide may account for the early inhibition of BaP-TPA carcinogenesis by nicotine at high doses (79).

Nicotine was found to enhance tumorigenic potential of 7, 12-Dimethylbenz [a] anthracene (DMBA) in hamsters. Application of sesame oil (control), 6% nicotine, 1% DMBA, or 1% DMBA plus 6% nicotine to the cheek pouches of male golden Syrian hamsters three times weekly for 12 weeks resulted in changes of the mucosa indicative of an effect of nicotine on DMBA tumor production. Cheek pouches from groups receiving sesame oil and nicotine appeared normal up to termination of treatment. By week 12, tumors of the cheek pouches were observed in the DMBA and DMBA plus nicotine groups, with the highest frequency occurring in the DMBA plus nicotine group. Microscopically, more invasive carcinomas and a greater degree of dysplasia were observed in lesions of the same size from the DMBA plus nicotine group than in lesions from the DMBA group. These results may be a chronic reaction to irritation caused by the nicotine present (80).

Nicotine was found to enhance stomach carcinogenicity induced by N-methyl-N-nitro- N-nitrosoguanidine (MNNG) following subcutaneous administration of 0.5 mg/kg nicotine 3 times weekly for 8 months to rats (81), and nicotine N-oxide (trans isomer and racemic mixture) significantly increased the frequency of forestomach tumors in rats initially treated with N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) (82). Similarly, application of 0.001% 4-(N-methyl-N-nitrosamine)-1-(3-pyridyl)-1-butanone (NNK) in combination with 6% nicotine to the cheek pouches of male golden Syrian hamsters three times weekly for 13 months produced a greater frequency in alterations in the mucosa of the forestomach (hyperplasia, hyperkeratosis and neoplasia) than in animals treated with NNK alone. In the same study, similar applications of

0.01% N-nitrosonornicotine (NNN) in combination with 6% nicotine resulted in a greater frequency of pathologic changes to the cheek pouch mucosa (hyperplasia, hyperkeratosis and moderate dysplasia) than in animals treated with NNN alone (83). Cotinine, however, had no effect on the incidence of forestomach tumors in the FANFT model. None of the metabolites of nicotine were found to enhance urinary bladder tumors, and nicotine N-oxide was shown to actually reduce the incidence of these tumors (82). In contrast, nicotine did not enhance the carcinogenicity of N-butyl-N-(4-hydroxylbutyl) nitrosamine (BBN), a potent carcinogen in the urinary bladder, or modify the incidence of N-nitrosomethylurea (NMU)-induced mammary tumors in rats (84,85).

Tobacco-specific nitrosamines (TSNAs), which are formed from nicotine and other tobacco alkaloids, have been implicated to be likely causative agents of cancers of the lung, oral cavity esophagus and pancreas in people who use tobacco products (86). N-nitroso-nornicotine (NNN), 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) have been shown to be the most carcinogenic tobacco-specific nitrosamines in animals. These and other nitrosamines form readily by nitrosation of secondary and tertiary amines.

The presence of TSNAs in saliva was determined following use of nicotine chewing gum that contained 380 ng TSNA/g of gum. The results of this evaluation found no indication of *in vivo* nitrosation, but rather that the concentration of TSNAs in saliva was due to the preformed TSNAs in the gum (87). In contrast, the ability of bacteria to catalyze the nitrosation of amines was reported from an *in vitro* assay in which incubation of chewing tobacco with human saliva resulted in the formation of TSNAs (88). However, the content of preformed NNN in the chewing tobacco that could have been easily extracted into the saliva was not discussed. Simulated *in vivo* conditions of endogenous nitrosation of nicotine have also been studied and no evidence to support such endogenous nitrosation of nicotine was found (89). From this study the investigators concluded that exposure to NNN results only from use of tobacco products containing preformed N-nitroso compounds and not from *in vivo* nitrosation of nicotine per se. More recently, although one study suggested evidence for endogenous formation of tobacco-specific nitrosamines in rats (90), a similar evaluation in humans concluded that the nitrosamine, 4-(methyl-nitrosamino)-4-(3-pyridyl)-butyric acid (iso-NNAC) in smoker's urine results from exposure to the preformed compound in mainstream cigarette smoke and not from endogenous nitrosation of nicotine and its metabolites (91).

In another study, which was conducted to determine the persistence of several TSNAs in human subjects who had quit smoking with and without the use of nicotine patch, there was no evidence for endogenous formation of TSNAs. If endogenous formation of TSNAs were occurring, higher levels of TSNA metabolites would have been observed in subjects using the nicotine patch in comparison to subject not using the patch (92).

In conclusion, neither nicotine nor its primary metabolite, cotinine, have been shown to be carcinogenic. However, nicotine and nicotine N-oxide may have a cocarcinogenic potential under certain conditions.

Local Tolerance:

Limited information is available in the scientific literature on the effect of nicotine replacement therapy (NRT) products on the oral mucosa, particularly with regard to direct effects

at the site of application. In one study, which was conducted to assess the effect of a 2 mg nicotine sublingual tablet on the oral mucosa of human subjects over a 3 to 6 month period of use, it was concluded that the sublingual tablet was a safe dosage form of NRT. No long-term adverse effects on the oral mucosa were observed and lesions that did occur during the exposure period were transient and reversible (93). In addition, studies that were conducted to evaluate the ability of nicotine to enhance the tumorigenic effect of DMBA or the pathologic effects of NNN on the oral mucosa of hamsters demonstrated that application nicotine alone for periods of 12 weeks to 13 months had no apparent adverse effect on the oral mucosa of hamsters (80,83).

Nicotine Degradation Products:

Cotinine and Nicotine N-Oxide:

Stability analyses of Nicotine Polacrilex Lozenges revealed the presence of the degradation products, cotinine, (1'R,2'S)-nicotine-1'-N-oxide, and (1'S,2'S)-nicotine-1'-N-oxide at concentrations that could result in potential maximum daily exposures of up to 640, 800, and 800 mcg/day (12.8, 16.0, 16.0 mcg/kg/day), respectively. Review of scientific literature reveals that cotinine and nicotine N-oxide are naturally-occurring metabolites of nicotine in humans and animals. Nicotine is primarily metabolized by the liver in humans, rabbits, guinea-pigs and rats to cotinine and nicotine N-oxide. The major metabolite, cotinine accounts for, on average, 80 to 90% of nicotine metabolism, while nicotine N-oxide accounts for approximately 5% of nicotine metabolism (94). Both compounds are formed by two independent oxidative pathways and are precursors for other metabolic products. In humans primarily CYP2A6 and/or CYP2B6 have been associated with nicotine metabolism to cotinine, while a minor contribution is attributed to CYP2D6 (11,12).

Myosamine:

Analyses of Nicotine Polacrilex Lozenges also revealed the presence of the degradation product, myosmine at a concentration that could result in a potential maximum daily exposure of 800 mcg/day (16.0 mcg/kg/day). Myosmine has been observed as a minor alkaloid in tobacco (95). The base is optically inactive and smells intensely of mice (the reason for its name). It is a weaker base than nicotine and it differs structurally from nicotine by lacking the methyl group on the nitrogen of the pyrrolidine ring, which has been converted to a pyrroline by a double bond on the two carbons adjacent to the pyridine ring.

Limited information has been published in the scientific literature regarding the toxicity of myosmine. It has a reported intraperitoneal LD_{50} of 190 mg/kg in rats, which is six-fold that of nicotine (96). Similarly, the approximate oral LD_{50} of myosmine in rats is 1875 mg/kg, in comparison to that for nicotine, which is 188 mg/kg (96). When evaluated for mutagenic potential in the *Escherichia coli* pol A+/A- test, myosmine induced repairable DNA damage; however, when tested in the Ames assay with *Salmonella typhimurium* using strains TA98, TA100 and TA1537, myosmine exhibited no mutagenic activity with or without metabolic activation (62). Additionally, when tested at concentrations of 62-250 mcg/ml, myosmine had no influence on the spontaneous frequency of sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (67).

The effect myosmine and other nicotine alkaloids on microcirculation were determined in a variety of rat tissues, including skeletal muscle; skin and mesentery (97). Myosmine at high doses (10^{-1} M) had the weakest vasoconstrictory effect on the mesentery vascular bed. Blood flow and velocity were reduced at lower doses; at higher doses they increased. The vasoconstriction elicited by myosmine (10^{-2} M) was minimal in the large arterioles of the skeletal muscle.

Conclusion:

Each Nicotine Polacrilex lozenge contains either 2 mg or 4 mg of nicotine. Use consists of slowly dissolving one lozenge in the mouth as needed to reduce smoking withdrawal symptoms, with a recommendation to repeat use at intervals ranging from every 1.5 to 8 hours depending on the phase of use. The standard therapy consists of 12 weeks.

The general pharmacology, pharmacokinetic and toxicology profile of nicotine in animals has been largely superseded by the extensive human experience with this agent, and this has been taken into account in the recommended posology. Nicotine toxicity reflects an exaggeration of it pharmacological activity. The principal metabolites of nicotine, as well as the degradation products identified in Nicotine Polacrilex Logenges, show little pharmacological activity and have not been demonstrated to produce toxic effects.

There are safety concerns regarding neonatal exposure to nicotine in humans. For this reason, the advice regarding use of Nicotine Polacrilex Logenges during pregnancy and lactation described in the product labelling is considered by the sponsor to be appropriate, in that use by pregnant women should be subject to a risk benefit assessment by a physician. However, class labeling for OTC nicotine products is currently under review advising women that nicotine, although not as harmful as cigarette smoking, may not be without risk to a developing fetus.

Evaluation of the mutagenic potential of a range of nicotine concentrations in a variety of *in vitro* and *in vivo* mutagenicity tests has shown that nicotine was not mutagenic in appropriate assays. The majority of evidence also indicates that nicotine and its primary metabolite, cotinine, are not carcinogenic. Although, the results of several studies indicate that nicotine and nicotine N-oxide may, under certain conditions, possess a cofactor or cocarcinogenic potential. Additionally, although it has been shown that TSNA occur in tobacco products containing nicotine and related secondary amines, there is no clear evidence that such compounds are formed *in vivo* in humans from use of nicotine replacement therapy products.

No significant effects on the oral mucosa are anticipated with use of Nicotine Polacrilex Logenges. Use of a similar product containing nicotine was shown to be well tolerated in humans over a 3 to 6 month period of use, and preclinical studies have demonstrated that oral application of nicotine for periods up to 13 months had no apparent adverse effect on the oral mucosa.

In conclusion, there is extensive animal and human experience with nicotine replacement products. Nicotine Polacrilex Logenges appear to be safe from a toxicological perspective for the proposed indication. However, the use of Nicotine Polacrilex Logenges during preganacy may not be without risk. Specific labeling for this and other OTC nicotine replacement products is warranted, and is currently under review by the Office of Over-The-Counter Drugs.

LABELING (Package Insert):

Because of animal studies showing nicotine-induced alterations during fetal brain development, the following labeling proposed by the sponsor is currently under review by the Office of Over-The-Counter Drugs:

"If you are pregnant or breast-feeding, _____

_____

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RECOMMENDATIONS:

Based on the extensive animal and human experience with nicotine replacement therapy, the submission NDA #21-330 (Nicotine Polacrilex Logenges, 2 mg and 4 mg) is approvable. Changes to the current labeling are recommended and should include a statement to the effect that nicotine use during pregnancy is not without risk. This issue is currently under review by the Office of Over-The-Counter Drugs.

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Supervisory Pharmacologist

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/s/

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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Supplement to Original Review

Thomas Papoian, Ph.D.
July 26, 2001

NDA #21-330

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SPONSOR: SmithKline Beecham Consumer Healthcare, L.P.
Parsippany, NJ

DRUG: Nicotine Polacrilex Lozenges, 2 mg and 4 mg

BACKGROUND:

There is a substantial body of literature that has examined the relationship between maternal smoking and developmental effects in both animals and humans. Much of the evidence implicates exposure to components of cigarette smoke as a major risk factor for intrauterine growth retardation and sudden infant death syndrome (SIDS). The role of nicotine as the primary component that is responsible requires further examination given the possible use of nicotine replacement therapy during pregnancy. For this purpose, a brief review follows of the most recent literature examining the relationship between exposure to nicotine during the perinatal period and the development of neurological effects, particularly those associated with SIDS. This possible relationship was not addressed in the original Pharmacology and Toxicology review dated February 20, 2001, and is included here as a supplement to the original review.

Literature Review: Possible Relationship Between Exposure to Nicotine During Pregnancy and Development of Sudden Infant Death Syndrome (SIDS):

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under one year of age that remains unexplained after a thorough case investigation, including the performance of a complete autopsy, examination of the death scene, and review of the clinical history (Willinger *et al.*, 1991). Prone sleeping position, overheating, and smoking have been identified as the most important factors that can be modified through public health intervention (reviewed in Anderson and Cook, 1997).

The single largest modifiable risk for pregnancy-related morbidity and mortality in the U.S. has been identified as cigarette smoking (reviewed in Dempsey and Benowitz, 2001). It has long been known that smoking during pregnancy results in intrauterine growth retardation. The average reduction in infant birth weight from smoking mothers has been reported to be 200 gms

with resultant increased risk of morbidity and mortality (Miller, 1992). In one study of 360,000 Missouri residents, it was estimated that if all pregnant women stopped smoking, the number of fetal and infant deaths would be reduced by about 10% (Kleinman *et al.*, 1988).

More recent epidemiological studies have shown that smoking during pregnancy and nursing is a major and independent risk factor for SIDS (reviewed in Kleinman *et al.*, 1988; Milerad and Sundell, 1993). A recent review of the 32 relevant publications in the scientific literature concluded that maternal smoking doubles the risk of SIDS (Anderson and Cook, 1997). The incidence of SIDS increases in proportion to the amount of cigarettes smoked, and the time of death coincides with high levels of nicotine metabolites in pericardial fluids in almost half of the infants that died of SIDS (reviewed in Milerad *et al.*, 1995). Since prenatal exposure to smoking is also generally associated with a postnatal smoking environment, the role of smoking during pregnancy as a risk for SIDS may be difficult to resolve using epidemiology alone (Anderson and Cook, 1997). Although much of the association between smoking and SIDS can be attributed to secondary smoke from the household, a significant intrauterine effect of smoking remains (Anderson and Cook, 1997).

Cigarette smoke contains thousands of chemicals, some of which are known to be fetal toxins, such as carbon monoxide, lead, and nicotine (Dempsey and Benowitz, 2001). Nicotine is a potent pharmacological agent that binds to a single class of $\alpha 4/\beta 2$ nicotinic cholinergic receptors located in the brain, autonomic ganglia, adrenal medulla, and neuromuscular junctions. Nicotine increases heart rate and myocardial contractility, constricts blood vessels, and increases blood pressure (Dempsey and Benowitz, 2001). Nicotine easily crosses the placental membrane and can compromise uteroplacental blood flow, an effect commonly cited as the mechanism responsible for the fetal growth retardation associated with smoking (reviewed in Milerad and Sundell, 1993; Dempsey and Benowitz, 2001).

However, studies conducted in animals using doses of nicotine that do not cause hypoxia or ischemia have shown that the primary target organ for the toxic effects of cigarette smoking and nicotine is thought to be the central nervous system (CNS) (Kinney *et al.*, 1993; Slotkin *et al.*, 1995, 1999, 2000; Dempsey and Benowitz, 2001). This evidence indicates that the adverse effects of smoking on neurological outcome are not secondary to fetal hypoxia-ischemia, and that nicotine may be directly toxic to the developing brain (reviewed in Kinney *et al.*, 1993).

The development of the CNS is a complex program involving the sequential development of neurogenesis and synaptogenesis (Dempsey and Benowitz, 2001). Neurogenesis begins with cell proliferation followed by cellular differentiation of neurons, including their migration and configuration of cytoarchitecture. Synaptogenesis involves the process of events required for the development of synaptic competence, including receptor expression, synthesis of and response to neurotransmitters, and postreceptor signaling events.

These neurogenic and synaptogenic events are determined during gestation. Studies with human fetuses have shown that the highest level of nicotine binding in the human brainstem tegmentum occurs during midgestation, a developmental period most likely to be vulnerable to the harmful effects of nicotine in maternal cigarette smoke (Kinney *et al.*, 1993). Inappropriate stimulation during this period has been shown in fetal rats to prematurely terminate cell proliferation and initiate cell differentiation in the developing CNS, resulting in a reduced number of neurons in specific regions of the brain (reviewed in Slotkin *et al.*, 1987; Slotkin, 1998; Dempsey and Benowitz, 2001). Behavioral studies in rats have shown that neurobehavioral alterations by nicotine occurs at doses that do not produce growth retardation

(reviewed in Slotkin, 1998). Such evidence has been interpreted to indicate that nicotine is a neuroteratogen (Slotkin *et al.*, 1987; Slotkin, 1998; Dempsey and Benowitz, 2001).

Many infants who have died of SIDS have been reported to have brain stem gliosis and elevated hypoxanthine levels in the vitreous humor, findings that suggest prolonged hypoxic events before death (reviewed in Milerad *et al.*, 1995). As mentioned above, human fetuses at midgestation have high concentrations of nicotine-binding sites in brainstem tegmentum nuclei, an area of the brain the controls cardiorespiratory integration, arousal, attention, rapid-eye movement sleep, and somatic motor control (Kinney *et al.*, 1993; Fewell and Smith, 1998). Impaired cardiorespiratory function and an inability to recover from prolonged sleep apnea has been postulated to be a principal cause of SIDS (Milerad and Sundell, 1993; Anderson and Cook, 1997; Fewell and Smith, 1998). One possible consequence of perinatal exposure to nicotine has been thought to be a change in the protective response that normally acts to prevent severe hypoxia and death during prolonged sleep apnea (Fewell and Smith, 1998). To examine this hypothesis, several studies have been conducted in animals to examine whether perinatal exposure to nicotine impairs the ability of newborn animals to autoresusitate from apnea induced by hypoxia.

In one of the first studies reported to examine this effect (Slotkin TA *et al.*, 1995), pregnant rats were given nicotine infusions at doses of 2 mg/kg/day and 6 mg/kg/day from gestation day 5 through parturition (gestation day 22). These doses produce plasma levels of nicotine similar to those seen in average and heavy smokers, respectively. Nicotine was administered by minipumps to avoid hypoxia and ischemia. The day after birth, animals in the high dose group showed increased mortality to a hypoxic challenge, and were found to be deficient in adrenomedullary catecholamine release, a function required to maintain neonatal cardiac rhythm during hypoxia. It was concluded from these studies that the nicotine-induced loss of the adrenomedullary release in response to hypoxia was responsible for the increased mortality seen during hypoxia. Other studies have shown that nicotine infusions to pregnant rats at doses of 6 mg/kg/day throughout gestation to day 5 postpartum resulted in an inability in pups to autoresuscitate from primary apnea in the presence of anoxic conditions (Fewell and Smith, 1998). The authors concluded that perinatal exposure to nicotine produced an impairment of the protective responses that terminate apnea and restore normal tidal ventilation.

Subsequent studies using the same perinatal rat model (gestation day 5 through parturition) have shown that cardiac M2-muscarinic cholinergic receptors, which are responsible for inhibitory autonomic actions to the sinoatrial node, were enhanced in nicotine-treated rats (Slotkin *et al.*, 1999). However, when these investigators exposed Rhesus monkeys to environmental tobacco smoke (ETS) during the perinatal period (last gestation to early neonatal period), neither decreases in cardiac beta-adrenergic receptor binding nor increases in m2-muscarinic receptors were found (Slotkin *et al.*, 2000). It was thought that the differences between the rat and the monkey were possibly due to species differences, amounts of nicotine delivered, or to exposure to different developmental periods (rats were exposed during all three trimesters, whereas monkeys were exposed only during the third trimester and the postnatal period). When the study was repeated in rats using exposure to ETS during the prenatal and postnatal periods, it was found that adenylate cyclase activity, a measure of cardiorespiratory function through its connection to stimulatory and inhibitory neurotransmitter receptors, was changed in both the prenatal and postnatal periods, but principally in the postnatal period (Slotkin *et al.*, 2001). These results indicated that vulnerability to nicotine's effects on

cardiorespiratory function may extend into the postnatal period, but that effects during the prenatal period could not be excluded.

Different investigators examined the effect of nicotine exposure *in utero* on the development of breathing control during early postnatal life in rats (Bamford *et al.*, 1996). Pregnant rats received nicotine using osmotic minipumps at doses of 6 mg/kg/day throughout gestation and for one week postnatally. Ventilatory responses of newborn rats to hypoxic conditions of 10% or 15% oxygen were measured. Results showed that nicotine exposure did not have a measurable effect on respiratory responses to moderate levels of hypoxia. Further studies in rats by the same investigators using higher doses of nicotine (12 mg/kg/day) throughout gestation and one week postnatally did not show differences between nicotine and control groups in baseline heart rates, respiratory rates, or gasping responses to anoxia (0% oxygen) (Schuen *et al.*, 1997). It was concluded that responses to anoxia were not affected by prenatal high-dose nicotine. However, these same investigators did find that perinatal exposure to nicotine in rats (gestation day 3 to postpartum day 8) resulted in an inability of 3 day old rats, but not 8 or 18 day old rats, to reduce ventilatory rates in response to 100% oxygen, a response mediated by chemoreception of the carotid body (Bamford and Carroll, 1999). It was concluded that nicotine exposure may have affected central respiratory integration of chemoreceptor input, but responses to hypoxic challenges were normal, indicating that the effects of nicotine were not acting directly on peripheral chemoreceptors.

Newborn lambs have been used to examine the relationship between exposure to nicotine shortly after birth and the possible development of SIDS. In one study, newborn lambs (mean ages of 7-27 days) on ventilation were given infusions of nicotine at 0.5 μg/kg/min. Peripheral chemoreceptor activity was stimulated by hypoxia (10% oxygen) and ventilatory measurements performed (Milerad *et al.*, 1995). Results showed that nicotine attenuated the early (1-3 min) ventilatory response to hypoxia. These results indicated to the investigators that the reduced ventilatory response to hypoxia was a result of altered chemoreceptor oxygen sensitivity or on processing of the chemoreceptor input, effects related to the central control of breathing. Further studies by the same investigators used 5 day old lambs to measure the effect of a short-term infusion of nicotine (0.5 μg/kg/min) on arousal to hypoxia (Hafstrom *et al.*, 2000). Results showed that arousal from quiet sleep was significantly delayed during nicotine infusion from that seen in the same animal during saline infusion. It was concluded that a brief exposure of newborn lambs to nicotine delays arousal in response to acute hypoxia during quiet sleep, findings with relevance for SIDS.

There is one report of a deficient hypoxic awakening response in infants of smoking mothers (Lewis and Bosque, 1995). In this study, 2-3 month old infants from smoking and nonsmoking mothers were studied for ventilatory and awakening responses to hypoxia (17%, 15%, and 13% inspired oxygen). Results showed that more infants of smokers failed to awake with hypoxia than did control infants (54% vs 15%, respectively). This difference occurred even though there was no difference between the two groups in the awakening threshold for carbon dioxide. It was concluded that the peripheral and central chemoreceptors are functioning, but that the brain stem-mediated hypoxic arousal response was deficient.

Several studies in animals have shown that exposure to nicotine *in utero* upregulates nicotine binding to nicotinic receptors in the brain by a mechanism that is not clear (reviewed in Nachmanoff, 1998). It was hypothesized that infants dying of SIDS may also have upregulation nicotine receptors in the brainstem, a finding that may be related to the altered regulation of

cardiorespiratory control and arousal when compared to control infants. When nicotine binding was examined in 14 regions of brainstem autopsy specimens from SIDS infants, control infants, and infants with chronic oxygenation disorders, it was found that there were no difference in nicotine binding between the groups. However, when the cases were stratified by a history of maternal smoking during pregnancy, it was found there was no expected increase (upregulation) on nicotinic receptors in SIDS infants in three nuclei related to arousal or cardiorespiratory control, as was found in control infants which showed the expected upregulation in these sites. It was concluded that alterations in nicotinic receptor binding in brainstem arousal circuits impairs protective arousal circuits, predisposing infants to sudden death when faced with a life-threatening hypoxic challenge during sleep.

In a recent review of the risks and benefits of nicotine as an aid for smoking cessation during pregnancy, Dempsy and Benowitz (2001) concluded that the risk of exposure during pregnancy to the many harmful substances contained in cigarette smoke is greater than the risk of exposure to pure nicotine. However, they also concluded that the use of nicotine replacement therapy (NRT) is not without potential risks as well, although they state that the use of NRT during pregnancy is reasonable based on the minimal effects of nicotine upon the maternal and fetal cardiovascular systems. Intermittent delivery formulations (gum, spray, or inhaler) are preferred over continuous delivery system (patch) because of the lower total dose delivered. The authors recommend that the efficacy of NRT for smoking cessation should be studied during pregnancy. This is based on the rationale that no pregnant woman should take NRT unless there is personal benefit. The authors also state that based on the animal studies that have shown fetal risk associated with nicotine exposure, including the possible link to SIDS, the safety of long-term nicotine exposure be studied, possibly through the creation of a pregnancy registry that collects outcome data from individual providers and hospital services. Such large studies using pregnant women taking NRT are necessary given the infrequent nature of perinatal events such as SIDS.

In summary, it is well established that cigarette smoking during pregnancy results in fetal growth retardation and is an independent risk factor for SIDS. However, since prenatal exposure to smoking is also generally associated with a postnatal smoking environment, the role of smoking during pregnancy as a risk for SIDS may be more difficult to resolve. Although cigarette smoke contains many known fetal toxins, the evidence that the pharmacological active ingredient nicotine is the component responsible for these effects is derived mostly from animal studies. These animal data have shown that nicotine may be directly toxic to the developing brain at a time of gestation in which nicotine-binding sites in areas of the brain controlling cardiorespiratory integration are maximally expressed in both animals and humans. It is thought that exposure to nicotine during this period may change the protective response that normally acts to prevent hypoxia and death during sleep apnea. Early studies in rats showed that perinatal exposure to nicotine produced an impairment of the protective responses that terminate apnea and restore normal tidal ventilation. However, studies by other investigators in rats exposed perinatally to nicotine and in Rhesus monkeys exposed perinatally to environmental tobacco smoke failed to confirm the early rat findings, although in rats ventilatory rates in response to 100% oxygen were reduced. Additional studies in newborn lambs and human infants showed an effect of exposure to smoking or nicotine on reducing the awakening response to hypoxia. This evidence supported the role of nicotine exposure as a possible risk for SIDS. However, whether exposure to nicotine *in utero* or exposure postnatally is the period of primary vulnerability has

been difficult to resolve. Although it is generally agreed that cigarette smoke is more harmful than nicotine, exposure to nicotine during pregnancy may not be without risk. Therefore, creation of a [redacted] ls may serve to establish the safety of nicotine exposure during pregnancy, particularly in elucidating its role as a potential risk for SIDS.

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RECOMMENDATIONS:

There is a reasonable role for the pharmaceutical manufacturers of nicotine replacement products to assist in collection of data from pregnant women exposed to nicotine. OTC has drafted several recommendations asking companies who market OTC nicotine replacement therapies (NRT) to conduct additional studies and obtain additional data from pregnant women who use NRT. One specific recommendation drafted by OTC is to ask these companies to:

[redacted]

Given the data in the published literature described above on the possible association between exposure to nicotine and developmental effects, including a possible increased risk for sudden infant death syndrome (SIDS), the OTC recommendation should be modified as follows:

[redacted] ve

[redacted]

Thomas Papoian, Ph.D.
Supervisory Pharmacologist

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Supplement to Original Review

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