

B. INDUSTRY RESEARCH ON THE DRUG EFFECTS OF NICOTINE

The tobacco industry has conducted and funded extensive research to characterize nicotine's addictive potential and properties. This research includes studies on nicotine's absorption into the bodies of tobacco users, its effects on behavior, and its effects on the brain and endocrine systems.²⁴⁰ Sections II.B., C., and D. detail the extensive research conducted and funded by the tobacco industry on: 1) nicotine's pharmacological effects, § II.B., *infra*; 2) how consumers use tobacco products to obtain an adequate dose of nicotine, § II.C., *infra*; and 3) how to manipulate nicotine delivery from tobacco to provide an adequate dose to consumers, § II.D., *infra*.^{240a}

²⁴⁰ The long history of tobacco and nicotine use for pharmacological purposes is also well known to the tobacco industry. Larson PS, Silvette H. Medical uses of tobacco (past and present), (funded by a grant from the Tobacco Industry Research Committee and presented at industry-sponsored symposium). In: VonEuler, ed. *Tobacco Alkaloids and Related Compounds*. New York, NY: Pergamon Press; 1965:3-11.

See also Cohen, note 183, *supra*, at p. 1.

^{240a} The extent of the industry's research on nicotine pharmacology is very likely to be even greater than that reflected in this section. According to a recent report in the *New York Times*, Philip Morris conducted internal research on nicotine's pharmacological effects on smokers from the late 1960's to the mid-1980's. The *Times* reported that Charles Wall, a Philip Morris lawyer, confirmed that company documents showed that Philip Morris carried out extensive research on nicotine over many years. Hiltz PJ. "Documents Disclose Philip Morris Studied Nicotine's Effect on Body." *New York Times*. June 8, 1995. Documents later disclosed by Congress provide detailed evidence of Philip Morris' long-term research on nicotine pharmacology, including studies to isolate and characterize nicotine receptors in the central nervous system, the effects of nicotine/smoking on the electrical activity of the brain, the effects of nicotine on human and animal behavior, self-administration of nicotine by rats, nicotine discrimination in rats, nicotine tolerance, and the effects of nicotine administration on human physiologic function, including the relationship between blood nicotine levels and central nervous system activity. 141 Cong. Rec. H7470-76 (daily ed. July 24, 1995); 141 Cong. Rec. H7646-83 (daily ed. July 25, 1995). Philip Morris has not contested the authenticity of these documents. R.J. Reynolds, too, appears to have conducted extensive research on nicotine pharmacology that is not fully reflected here. In response to questions about that company's research on nicotine, a spokeswoman for R.J. Reynolds Tobacco Company stated that "[w]e've not only done research on the pharmacological effects of nicotine but we've published it in at least 250 peer-reviewed journals and symposia. We're extremely proud of the quality and number of the studies." Collins G. "Legal Attack on Tobacco Intensifies." *New York Times*. June 9, 1995.

It is important to understand why the tobacco industry has conducted this research. Tobacco industry documents show that the industry research described in the following sections was undertaken because industry officials strongly suspected, more than 30 years ago, that nicotine's pharmacological effects were vital to the successful marketing of tobacco. For example, internal BATCO documents disclose that the major BATCO-sponsored nicotine studies completed or underway in the early 1960's were undertaken "to elucidate the effects of nicotine as a beneficent alkaloid drug"²⁴¹ because of the belief of Sir Charles Ellis, the leading BATCO scientist, that "we are in a nicotine rather than a tobacco industry."²⁴²

Another nicotine study commissioned by BATCO in the early 1960's similarly reveals that industry research on nicotine's pharmacological effects was undertaken because of the industry's understanding that consumers use tobacco to obtain those effects:

There is increasing evidence that nicotine is the key factor in controlling, through the central nervous system, a number of the beneficial effects of tobacco smoke . . . Detailed knowledge of these effects of nicotine in the body

²⁴¹ See Ellis, note 232, *supra*, at p. 16. On the same page Ellis describes upcoming research "to investigate whether cigarette smoke produces effects on the central nervous system characteristic of tranquilising or stimulating drugs and, if so, to see if such activity is due solely to nicotine."

²⁴² Johnson RR. *Comments on nicotine*. June 30, 1963. Pages 10-11. This document goes on to reveal that these studies on nicotine's pharmacological effects were part of a broader research initiative that was being conducted by the industry and included altering nicotine delivery:

The Southampton group is going to be doing a large amount of work on nicotine, and for some good reasons. To summarize:

Project ARIEL [a cigarette alternative developed by BATCO] - This is dormant for the moment. The first samples tried gave a tremendous kick, even though the nicotine delivery was quite small. It would appear that the project will be reinitiated within a few months.

Dr. S.R. Evelyn is presently investigating the absorption of extractable and non-extractable nicotine in the mouth . . .

Dr. J.D. Backhurst is setting up an analysis for pH of whole smoke on a puff-by-puff basis. This correlates with his previous interest in extractable nicotine.

Mr. H.G. Horsewell continues to work with alkaline filter additives which selectively increase nicotine delivery.

*of a smoker is therefore of vital importance to the tobacco industry.*²⁴³

An annual report from the Council for Tobacco Research discloses that the research it funded on nicotine's pharmacology was designed to elucidate the effects of nicotine on the smoker's central nervous system:

*Most of the pharmacological studies currently being supported by The Council are concerned with the effects of nicotine and/or smoking on the central nervous system (the brain) with the object of learning more about why people like, want, or need to smoke.*²⁴⁴

The studies of nicotine's pharmacokinetics and pharmacodynamics described in § II.B., *infra*, were undertaken to assist the industry in marketing products that would satisfy tobacco users' nicotine requirements. This information relating to how nicotine acted in the body was needed by the industry for additional studies specifically designed to establish the dose of nicotine required by consumers, § II.C., *infra*. As noted in the report of one study whose purpose was to validate a method for assaying nicotine and a metabolite in urine:

*It can be concluded from the comparative studies that analysis of nicotine and cotinine in urine is likely to be a good indicator of whole body nicotine dose in man. This technique has an immediate and direct relevance for . . . human behavioural studies in the assessment of an individuals' [sic] nicotine dose in response to modification in cigarette design. [Emphasis added.]*²⁴⁵

²⁴³ Geissbuhler H, Haselbach C. *The Fate of Nicotine in the Body*. Battelle Memorial Institute. Geneva, Switzerland. May 1963. Page 1. Report prepared by Battelle for BATCO. (Hereafter cited as: BATCO. *The Fate of Nicotine in the Body*.)

²⁴⁴ Report of the Scientific Director, 1969-1970. Council for Tobacco Research-U.S.A. Page 13.

²⁴⁵ BATCO Group R&D Centre. *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose By Urinary Nicotine and Cotinine Measurement*. Report No. RD.1792. March 31, 1981. Page 1.

Industry documents related to other basic research studies on nicotine show a similar nexus with product development. For example, the report from a 1974 Brown and Williamson study of nicotine's brain effects states that:

The development of new products and the modification of existing ones requires that we have some knowledge of the smoker toward whom these efforts are directed. The work described in this report is focused on the acute, or immediate physiological response of

Thus, this research demonstrates the tobacco industry's fundamental interest in the dose of nicotine absorbed into the systemic circulation of the tobacco user (rather than simply the amount of nicotine necessary to deliver sensory effects to the mouth of the user.)

The ultimate purpose of the tobacco industry's studies on nicotine was to better understand the nicotine requirements of tobacco users and to develop products that delivered the desired pharmacological effects of nicotine. Philip Morris officials stated that the rationale for the company's extensive research program on nicotine pharmacology was that the information would

strengthen Philip Morris R&D capability in developing new and improved smoking products.^{245a}

Accordingly, the industry-sponsored studies described in the following sections provide further evidence that tobacco manufacturers intend to market their products to deliver the pharmacological effects of nicotine to consumers.²⁴⁶

smokers.

Brotzge RF, Kennedy JE. Brown and Williamson. *Human Smoking Studies: Acute Effect of Cigarette Smoke on Brain Wave Alpha Rhythm - First Report.* October 31, 1974. Report No. 74-20. Page 1.

Similarly, a 1974 BATCO study on nicotine's effects on brain electrical activity was intended to "help elucidate the mode of action of nicotine during smoking" so as to better understand smoker behavior in response to nicotine. BATCO Group Research & Development. Comer AK, Thornton RE. *Interaction of Smoke and the Smoker Part 3: The Effect of Cigarette Smoking on the Contingent Negative Variation.* Report No. RD.1164-R. December 12, 1974. Page 2.

^{245a} Memorandum from W.L. Dunn to T.S. Osdene-Plans and Objectives-1979. December 6, 1978. *In* 141 Cong. Rec. H7669 (daily ed. July 25, 1995).

²⁴⁶ The full citations for the references in notes 247 through 279 can be found in Appendix 4. Entries under the heading "OTHER" include studies sponsored by the Smokeless Tobacco Research Council (whose members include U.S. tobacco companies), Swedish Tobacco Co. (which has corporate relationships with both Pinkerton and U.S. Tobacco Co.), Svenska Tobaks (a subsidiary of Swedish Tobacco Co.), the Tobacco Advisory Council and the Tobacco Research Council of the U.K. (whose members included British-American Tobacco Co.), Imperial Tobacco Co. (which has corporate relationships with British-American Tobacco Co., and manufactures cigarettes that are marketed in the U.S.), Carreras Rothmans Ltd. (whose affiliated companies manufacture cigarettes that are marketed in the U.S.), Swiss Association of Cigarette Manufacturers (whose members include affiliates of U.S. tobacco companies, and the Canadian Tobacco Manufacturers Council (whose members include affiliates of U.S. tobacco companies).

1. Industry Research on Nicotine's Effects on the Brain

The tobacco industry has extensively studied, in its own laboratories and through grants or contracts to other laboratories, the effects of nicotine on the brain and other parts of the central nervous system, including the sites in the brain on which nicotine acts.²⁴⁷

²⁴⁷ COUNCIL FOR TOBACCO RESEARCH-USA

- Abood. Comparison of the binding of optically pure (-) and (+)-[3H]nicotine to rat brain membranes
- Abood. Electrophysiological, behavioral, and chemical evidence for a noncholinergic, stereospecific site for nicotine in rat brain
- Abood. Receptor binding characteristics of a 3H-labeled azetidone analogue of nicotine
- Abood. Tritiated methylcarbamylcholine a new radioligand for studying brain nicotinic receptors
- Abood. Evidence for a noncholinergic site for nicotine's action in brain: Psychopharmacological, electrophysiological and receptor binding studies
- Abood. Acute and chronic effects of nicotine in rats and evidence for a non-cholinergic site of action
- Andersson. Involvement of D1 dopamine receptors in the nicotine-induced neuro- endocrine effects and depletion of diencephalic catecholamine stores in the male rat
- Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenyhypophyseal hormones in the male rat
- Andersson. Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenyhypophyseal hormone secretion in the normal male rat
- Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat
- Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus
- Andersson. Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenyhypophyseal hormones
- Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat
- Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenyhypophyseal hormones and corticosterone
- Andersson. Effects of chronic exposure to cigarette smoke on amine levels and turnover in various hypothalamic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male rat
- Andersson. Mecamylamine pretreatment counteracts cigarette smoke induced changes in hypothalamic catecholamine neuron systems and in anterior pituitary function
- Bhagat. Effects of chronic administration of nicotine on storage and synthesis of noradrenaline in rat brain
- Bhagat. Influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat brain
- Bhagat. Effect of chronic administration of nicotine on the concentrations of adrenal enzymes involved in the synthesis and metabolism of adrenaline
- Bhattacharya. Influence of acute and chronic nicotine administration on EEG reactivity to drugs in rabbits: 2. Psychoactive agents
- Chance. A comparison of nicotine and structurally related compounds as discriminative stimuli
- Chang. Effect of chronic administration of nicotine on acetylcholinesterase activity in the hypothalamus and medulla oblongata of the rat brain An ultrastructural study
- Davies. Evidence for a noncholinergic nicotine receptor on human phagocytic leukocytes
- Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study
- Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain
- Essman. Changes in cholinergic activity and avoidance behavior by nicotine in differentially housed mice
- Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke
- Fuxe. Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors
- Grenhoff. Selective stimulation of limbic dopamine activity by nicotine
- Grenhoff. Chronic continuous nicotine treatment causes decreased burst firing of nigral dopamine neurons in rats partially hemitranssected at the meso-diencephalic junction
- Harfstrand. Distribution of nicotinic cholinergic receptors in the rat tel- and diencephalon: a quantitative receptor autoradiographical study using [3H]-acetylcholine, [alpha-125I]bungarotoxin and [3H]nicotine
- Harsing. Dopamine efflux from striatum after chronic nicotine: evidence for autoreceptor desensitization
- Huganir. Phosphorylation of the nicotinic acetylcholine receptor regulates its rate of desensitization
- Kawamura. Differential actions of m and n cholinergic agonists on the brainstem activating system
- Knapp. Action of nicotine on the ascending reticular activating system
- Kramer. The effect of nicotine on catecholaminergic storage vesicles
- Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance
- Lapin. Action of nicotine on accumbens dopamine and attenuation with repeated administration

- Lindstrom. Structural and functional heterogeneity of nicotinic receptors
- London. Glucose metabolism: An index of nicotine action in the brain
- Lowy. Antagonism by cholinergic drugs of behavioural effects in cats of an anticholinergic psychotomimetic drug and enhancement by nicotine
- Lukas. Heterogeneity of high-affinity nicotinic [³H]acetylcholine binding sites
- Lukas. Pharmacological distinctions between functional nicotinic acetylcholine receptors on the PC12 rat pheochromocytoma and the TE671 human medulloblastoma
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- Mitchell. Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotine
- Naftchi. Acute reduction of brain substance P induced by nicotine
- Nelsen. Chronic nicotine treatment in rats: 2. Electroencephalographic amplitude and variability changes occurring within and between structures
- Owman. Chronic nicotine treatment eliminates asymmetry in striatal glucose utilization following unilateral transection of the mesostriatal dopamine pathway in rats
- Pradhan. Effects of nicotine on self-stimulation in rats
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- Rosecrans. Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms
- Schaeppi. Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system
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- Sershen. Nicotinic Binding Sites in the brain: properties, regulation, and putative endogenous ligands
- Siegel. Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relationship to neuroendocrine function
- Silvette. The actions of nicotine on central nervous system functions
- Sorenson. The reducing agent dithiothreitol (DTT) does not abolish the inhibitory nicotinic response recorded from rat dorsolateral septal neurons
- Stadnicki. Nicotine changes in EEG and behavior after intravenous infusion in awake unrestrained cats
- Stadnicki. Nicotine infusion into the fourth ventricle of unrestrained cats: changes in EEG and behavior
- Stitzer. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists
- Sugiyama. [³H]Nicotine binding sites in developing fetal brains in rats
- Svensson. Effect of nicotine on dynamic function of brain catecholamine neurons
- Toth. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid
- Toth. Effect of nicotine on levels of extracellular amino acids in regions of the rat brain in vivo
- Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids
- Vincek. Synthesis of 4,4-ditritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer
- Westfall. Effect of nicotine and related substances upon amine levels in the brain
- Whiting. Expression of nicotinic acetylcholine receptor subtypes in brain and retina
- Wong. Pharmacology of nicotinic receptor-mediated inhibition in rat dorsolateral septal neurones
- Wong. A direct nicotinic receptor-mediated inhibition recorded intracellularly in vitro
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- Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications
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- Vezina. The effect of acute and repeated nicotine injections on brain dopamine activation: Comparisons with morphine and amphetamine
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- Bjercke. Anti-idiotypic antibody probes of neuronal nicotinic receptors
- Brazell. Effect of acute administration of nicotine on in vivo release of noradrenaline in the hippocampus of freely moving rats: a dose-response and antagonist study
- Collins. Modulation of Nicotine Receptors by Chronic Exposure to Nicotinic Agonists and Antagonists
- Gilbert. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie
- Lippiello. The Role of Desensitization in CNS Nicotinic receptor function

- Lippiello. Characterization of nicotinic receptors on cultured cortical neurons using anti-idiotypic antibodies and ligand binding
- Lippiello. The binding of L-[3H]nicotine to a single class of high affinity sites in rat brain membranes
- Lippiello. Identification of putative high affinity nicotinic receptors on cultured cortical neurons
- Lippiello. Kinetics and mechanism of L-[3H]nicotine binding to putative high affinity receptor sites in rat brain
- Marks. Downregulation of nicotinic receptor function after chronic nicotine infusion
- Mitchell. Nicotine-induced catecholamine synthesis after lesions to the dorsal or ventral noradrenergic bundle
- Mitchell. Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain
- Prince. Actions of the general anesthetic propofol (2,6- diisopropylphenol) on the binding of [3H] nicotine to rat cortical membranes
- Pritchard. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity
- Smith. Effects of chronic and subchronic nicotine on tyrosine hydroxylase activity in noradrenergic and dopaminergic neurones in the rat brain
- Wonnacott. Presynaptic actions of nicotine in the CNS
- BROWN AND WILLIAMSON TOBACCO CORPORATION, Unpublished**
- Brodzke. Human smoking studies: acute effect of cigarette smoke on brain wave alpha rhythm-first report
- BRITISH-AMERICAN TOBACCO COMPANY, LTD.**
- Golding. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation
- Golding. Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving
- BRITISH-AMERICAN TOBACCO COMPANY, LTD., Unpublished**
- Ayres. Notes from the GR & DC Nicotine Conference
- Comer. Interaction of smoke and the smoker part 3: the effect of cigarette smoking on the contingent negative variation
- BRITISH-AMERICAN TOBACCO COMPANY, LTD. Funded - Unpublished Battelle Studies**
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- Haselbach. A tentative hypothesis on nicotine addiction
- Hersch. Final report on project HIPPO I
- Libert. Report no 1 regarding project HIPPO II
- Wiley. Effects of nicotine on the central nervous system
- INDUSTRY SUPPORTED AMA/EDUCATIONAL AND RESEARCH FOUNDATION (ERF) STUDIES:**
- Murphree. Electroencephalographic changes in man following smoking
- Rosecrans. Brain area nicotine levels in male and female rats with different levels of spontaneous activity
- Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity
- Rosecrans. Brain area nicotine levels in male and female rats of two strains
- Schechter. Behavioral evidence for two types of cholinergic receptors in the C.N.S.
- Schechter. Effect of mecamylamine on discrimination between nicotine- and arecoline- produced cues
- Schechter. Nicotine as a discriminative cue in rats: inability of related drugs to produce a nicotine-like cueing effect
- Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine
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- Armitage. Pharmacological basis for the tobacco smoking habit
- Armitage. Some recent observations relating to the absorption of nicotine from tobacco smoke
- Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex
- Armitage. Nicotine, Smoking and cortical activation
- Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat
- Armitage. Effects of nicotine and some nicotine-like compounds injected into the cerebral ventricles of the cat
- Armitage. Further evidence relating to the mode of action of nicotine in the central nervous system
- Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour
- Bhagat. The effects of nicotine and other drugs on the release of injected 3H-norepinephrine and on endogenous norepinephrine levels in the rat brain
- Hall. Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb
- Morrison. A comparison of the effects of nicotine and physostigmine on a measure of activity in the rat
- Wesnes. Effects of scopolamine and nicotine on human rapid information processing performance
- Wesnes. The separate and combined effects of scopolamine and nicotine on human information processing
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- Adem. Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography
- Adem. Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres
- Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems
- Cohen. Monograph on the pharmacology and toxicology of nicotine and its role in tobacco smoking
- Copeland. A comparison of the binding of nicotine and nor nicotine stereoisomers to nicotinic binding sites in rat brain cortex

Mechanisms of action: receptors, neurotransmitters, and hormones. The tobacco industry has supported sophisticated studies to identify the sites and mechanisms of nicotine's actions, as well as how the structure of the brain itself is altered by nicotine's effects on nicotinic receptors. These studies have identified the receptors in the central nervous system on which nicotine acts; shown that nicotinic receptors present in the brain of both animals and man mediate the behavioral effects of nicotine; and sought to define the location and functional properties of these nicotinic receptors in the central nervous system.²⁴⁸

Falkeborn. Chronic nicotine exposure in rat: a behavioural and biochemical study of tolerance
 Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine
 Fuxe. Reduction of [3H]nicotine binding in hypothalamic and cortical membranes by dopamine D1 receptors
 Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor
 Grenhoff. Nicotinic effects on the firing pattern of midbrain dopamine neurons
 Hasenfratz. Smoking-related subjective and physiological changes: pre- to postpuff and pre- to post cigarette
 Hasenfratz. Post-lunch smoking for pleasure seeking or arousal maintenance?
 Knott. Effects of cigarette smoking on subjective and brain evoked responses to electrical pain stimulation
 Larsson. Comparative analysis of nicotine-like receptor-ligand interactions in rodent brain homogenate
 Larsson. In vitro binding of 3H-acetylcholine to nicotinic receptors in rodent and human brain
 Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area
 Nordberg. Effect of long-term nicotine treatment on [3H]nicotine binding sites in the rats brain
 Nordberg. Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs
 Nordberg. Studies of muscarinic and nicotinic binding sites in brain
 Perez de la Mora. Neurochemical effects of nicotine on glutamate and GABA mechanisms in the rat brain
 Slotkin. Developmental Effects of Nicotine
 Slotkin. Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways
 Svensson. Effect of nicotine on single cell activity in the noradrenergic nucleus locus coeruleus
 Zhang. Effects of chronic treatment with (+)- and (-)- nicotine on nicotinic acetylcholine receptors and N-methyl-D-aspartate receptors in rat brain

OTHER, Literature Review

Edwards. Smoking, nicotine and electrocortical activity

²⁴⁸ COUNCIL FOR TOBACCO RESEARCH-USA
 Abood. Comparison of the binding of optically pure (-)- and (+)-[3H]nicotine to rat brain membranes
 Abood. Electrophysiological, behavioral, and chemical evidence for a noncholinergic, stereospecific site for nicotine in rat brain
 Abood. Evidence for a noncholinergic site for nicotine's action in brain: Psychopharmacological, electrophysiological and receptor binding studies
 Abood. Tritiated methylcarbamylcholine a new radioligand for studying brain nicotinic receptors
 Andersson. Intravenous injections of nicotine induce very rapid and discrete reductions of hypothalamic catecholamine levels associated with increases of ACTH, vasopressin and prolactin secretion
 Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophysal hormones in the male rat
 Andersson. Nicotine-induced increases of norepinephrine turnover in discrete norepinephrine nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophysal hormones
 Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons
 Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems
 Britto. Immunohistochemical localization of nicotinic acetylcholine receptor subunits in the mesencephalon and diencephalon of the chick (Gallus gallus)
 Chance. A comparison of nicotine and structurally related compounds as discriminative stimuli
 Davies. Evidence for a noncholinergic nicotine receptor on human phagocytic leukocytes
 Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications
 Fuxe. Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors
 Harstrand. Distribution of nicotinic cholinergic receptors in the rat tel- and diencephalon: a quantitative receptor autoradiographical study using [3H]-acetylcholine, [alpha-125I]bungarotoxin and [3H]nicotine
 Haganir. Phosphorylation of the nicotinic acetylcholine receptor regulates its rate of desensitization

- Lapin. Action of nicotine on accumbens dopamine and attenuation with repeated administration
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- Mitchell. Increases in tyrosine hydroxylase messenger RNA in the locus coeruleus after a single dose of nicotine are followed by time- dependent increases in enzyme activity and noradrenaline release
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- Whiting. Expression of nicotinic acetylcholine receptor subtypes in brain and retina
- Wong. A direct nicotinic receptor-mediated inhibition recorded intracellularly in vitro
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- R. J. REYNOLDS COMPANY**
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- Collins. Modulation of Nicotine Receptors by Chronic Exposure to Nicotinic Agonists and Antagonists
- Lippiello. The Role of Desensitization in CNS Nicotinic receptor function
- Lippiello. Characterization of nicotinic receptors on cultured cortical neurons using anti-idiotypic antibodies and ligand binding
- Lippiello. Identification of putative high affinity nicotinic receptors on cultured cortical neurons
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- Lippiello. The binding of L-[3H]nicotine to a single class of high affinity sites in rat brain membranes
- Marks. Downregulation of nicotinic receptor function after chronic nicotine infusion
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- DeNoble. Brain Sites Involved in the Mediation of the Behavioral Effects of Intraventricularly Administered (-)-nicotine
- DeNoble. Manuscript—Brain Sites Involved in the Mediation of the Behavioral Effects of Intraventricularly Administered (-)-nicotine
- INDUSTRY SUPPORTED AMA/ERF STUDIES**
- Hirschhorn. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine
- Schechter. Behavioral evidence for two types of cholinergic receptors in the CNS
- Schechter. Effect of mecamylamine on discrimination between nicotine- and arecoline- produced cues
- Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine
- TOBACCO RESEARCH COUNCIL LABS, U.K.**
- Wesnes. The separate and combined effects of scopolamine and nicotine on human information processing
- Wesnes. Effects of scopolamine and nicotine on human rapid information processing performance
- OTHER**
- Adem. Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres
- Adem. Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography
- Copeland. A comparison of the binding of nicotine and nornicotine stereoisomers to nicotinic binding sites in rat brain cortex

Neurotransmitters. Tobacco industry studies have shown that nicotine and its metabolites produce neurochemical and metabolic effects in the brain.²⁴⁹

- Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine
 Fuxe. Reduction of [3H]nicotine binding in hypothalamic and cortical membranes by dopamine D1 receptors
 Larsson. In vitro binding of 3H-acetylcholine to nicotinic receptors in rodent and human brain
 Larsson. Comparative analysis of nicotine-like receptor-ligand interactions in rodent brain homogenate
 Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area
 Nordberg. Effect of long-term nicotine treatment on [3H]nicotine binding sites in the rat brain
 Nordberg. Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs
 Nordberg. Studies of muscarinic and nicotinic binding sites in brain
 Slotkin. Developmental Effects of Nicotine
 Svensson. Effect of nicotine on single cell activity in the noradrenergic nucleus
 Zhang. Effects of chronic treatment with (+)- and (-)- nicotine on nicotinic acetylcholine receptors and N-methyl-D-aspartate receptors in rat brain

²⁴⁹ COUNCIL FOR TOBACCO RESEARCH-USA

- Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems
 Andersson. Mecamylamine pretreatment counteracts cigarette smoke induced changes in hypothalamic catecholamine neuron systems and in anterior pituitary function
 Andersson. Intravenous injections of nicotine induce very rapid and discrete reductions of hypothalamic catecholamine levels associated with increases of ACTH, vasopressin and prolactin secretion
 Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat
 Andersson. Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophysal hormone secretion in the normal male rat
 Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophysal hormones in the male rat
 Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat. Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons
 Andersson. Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophysal hormones
 Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus
 Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophysal hormones and corticosterone
 Andersson. Effects of chronic exposure to cigarette smoke on amine levels and turnover in various hypothalamic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male rat
 Bhagat. Influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat-brain
 Bhagat. Effect of chronic administration of nicotine on the concentrations of adrenal enzymes involved in the synthesis and metabolism of adrenaline
 Bhagat. Effects of chronic administration of nicotine on storage and synthesis of noradrenaline in rat brain
 Chang. Effect of chronic administration of nicotine on acetylcholinesterase activity in the hypothalamus and medulla oblongata of the rat brain. An ultrastructural study
 Chiou. The ability of various nicotinic agents to release acetylcholine from synaptic vesicles
 Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain
 Essman. Changes in cholinergic activity and avoidance behavior by nicotine in differentially housed mice
 Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke
 Grenhoff. Chronic continuous nicotine treatment causes decreased burst firing of nigral dopamine neurons in rats partially hemitranssected at the meso-diencephalic junction
 Grenhoff. Selective stimulation of limbic dopamine activity by nicotine
 Harsing. Dopamine efflux from striatum after chronic nicotine: evidence for autoreceptor desensitization
 Knapp. Action of nicotine on the ascending reticular activating system
 Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance
 Lapin. Action of nicotine on accumbens dopamine and attenuation with repeated administration
 Lowy. Antagonism by cholinergic drugs of behavioural effects in cats of an anticholinergic psychotomimetic drug and enhancement by nicotine
 Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro
 Mitchell. Increases in tyrosine hydroxylase messenger RNA in the locus coeruleus after a single dose of nicotine are followed by time-dependent increases in enzyme activity and noradrenaline release

These studies show that nicotine exerts its behavior modifying effects, in part, through the cascade of effects that are produced through nicotine's actions on existing brain chemicals. Industry-supported studies show that nicotine, like other addictive drugs, acts on dopaminergic receptors²⁵⁰ in the mesolimbic system to release

Mitchell. Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotine

Naftchi. Acute reduction of brain substance P induced by nicotine

Siegel. Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relationship to neuroendocrine function

Toth. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid

Toth. Effect of nicotine on levels of extracellular amino acids in regions of the rat brain in vivo

Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids

Westfall. Effect of nicotine and related substances upon amine levels in the brain

Westfall. Effect of nicotine and other drugs on the release of 3H-norepinephrine and 3H-dopamine from rat brain slices

R. J. REYNOLDS COMPANY

Brazell. Effect of acute administration of nicotine on in vivo release of noradrenaline in the hippocampus of freely moving rats: a dose-response and antagonist study

Mitchell. Nicotine-induced catecholamine synthesis after lesions to the dorsal or ventral noradrenergic bundle

Mitchell. Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain

Smith. Effects of chronic and subchronic nicotine on tyrosine hydroxylase activity in noradrenergic and dopaminergic neurones in the rat brain

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished

Haselbach. Tentative Hypothesis on Nicotine Addiction

Haselbach. Final Report on Project HIPPO II

INDUSTRY SUPPORTED SYMPOSIA

Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

Nordberg. Assessment of cholinergic neuronal activity in the brain

INDUSTRY SUPPORTED AMA/ERF STUDIES

Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine

TOBACCO RESEARCH COUNCIL LABS, U.K.

Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat

Armitage. Further evidence relating to the mode of action of nicotine in the central nervous system

Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour

Bhagat. The effects of nicotine and other drugs on the release of injected 3H-norepinephrine and on endogenous norepinephrine levels in the rat brain

OTHER

Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor

Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine neurons

Grenhoff. Nicotinic effects on the firing pattern of midbrain dopamine neurons

Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area

Nordberg. Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs

Perez de la Mora. Neurochemical effects of nicotine on glutamate and GABA mechanisms in the rat brain

Slotkin. Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways

OTHER, Literature Review

Edwards. Smoking, nicotine and electrocortical activity

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COUNCIL FOR TOBACCO RESEARCH-U.S.A.

Abood. Receptor binding characteristics of a 3H-labeled azetidene analogue of nicotine

Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus

Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophyseal hormones and corticosterone

Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat. Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons

Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat

Andersson. Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat

Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophyseal hormones in the male rat

Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain

dopamine, a chemical in the brain associated with pleasurable feelings.

Mood modification and EEG effects. In tobacco industry-sponsored trials, nicotine has been shown to induce both behavioral arousal and calming effects.²⁵¹ These effects have been correlated with

Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke

Grenhoff. Selective stimulation of limbic dopamine activity by nicotine

Harsing. N-type calcium channels are involved in the dopamine releasing effect of nicotine

Lapin. Action of nicotine on accumbens dopamine and attenuation with repeated administration

Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance

Westfall. Effect of nicotine and other drugs on the release of 3H-norepinephrine and 3H-dopamine from rat brain slices

R. J. REYNOLDS COMPANY

Lippiello. The role of desensitization in CNS nicotinic receptor function

Marks. Downregulation of nicotinic receptor function after chronic nicotine infusion

INDUSTRY SUPPORTED SYMPOSIA

Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

OTHER

Adem. Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres

Anderson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine-induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems

Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor

Grenhoff. Nicotinic effects on the firing pattern of midbrain dopamine neurons

Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area

²⁵¹ **COUNCIL FOR TOBACCO RESEARCH-USA**

Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Heimstra. The effects of deprivation of cigarette smoking on psychomotor performance

Marks. Genetics of nicotine response in four inbred strains of mice

Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats

Pradhan. Effects of nicotine on several schedules of behavior in rats

Schaepfi. Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system

Stadnicki. Nicotine infusion into the fourth ventricle of unrestrained cats: changes in EEG and behavior

Stadnicki. Nicotinic changes in EEG and behavior after intravenous infusion in awake unrestrained cats

Yamamoto. Nicotine-induced EEG and behavioral arousal

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Review

Silvette. The actions of nicotine on central nervous system functions

R. J. REYNOLDS COMPANY

Lippiello. Properties of putative nicotine receptors identified on cultured cortical neurons

Pritchard. Electroencephalographic effects of cigarette smoking

Robinson. The role of nicotine in tobacco use

BRITISH-AMERICAN TOBACCO COMPANY, LTD.

Golding. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation

Mangan. The effects of cigarette smoking on vigilance performance

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished

Corner. Interaction of Smoke and the Smoker Part 3: The Effect of Cigarette Smoking on the Contingent Negative Variation

Thornton. Some "Benefits" of Smoking

INDUSTRY SUPPORTED SYMPOSIA

Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

Wesnes. The effects of cigarette smoking and nicotine tablets upon human attention

INDUSTRY SUPPORTED AMA/ERF STUDIES

Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

TOBACCO RESEARCH COUNCIL LABS., U.K.

Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

Armitage. Nicotine, smoking and cortical activation

Hall. Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb

Morrison. Antagonism by antimuscarinic and ganglion-blocking drugs of some of the behavioural effects of nicotine

Morrison. The occurrence of tolerance to a central depressant effect of nicotine

Warwick. Experimental studies of the behavioural effects of nicotine

OTHER

electroencephalogram/electrocorticogram changes in electrical activity in the brain.²⁵² Whether nicotine provides a stimulating or calming effect depends on the dose of nicotine taken, the time elapsed since the last dose, and other factors.²⁵³

Cohen. Monograph on the "Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking Draft

Edwards. Evidence of more rapid stimulus evaluation following cigarette smoking

Golding. Effects of cigarette smoking on measures of arousal, response suppression, and excitation/inhibition balance

Nordberg. Effect of nicotine on passive avoidance behaviour and motoric activity in mice

²⁵² **COUNCIL FOR TOBACCO RESEARCH-USA**

Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain

Kawamura. Differential actions of m and n cholinergic agonists on the brainstem activating system

Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro

Nelsen. Chronic nicotine treatment in rats 2 Electroencephalographic amplitude and variability changes occurring within and between structures

Schaeppi. Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system

Stadnicki. Nicotine infusion into the fourth ventricle of unrestrained cats: changes in EEG and behavior

Stadnicki. Nicotinic changes in EEG and behavior after intravenous infusion in awake unrestrained cats

Yamamoto. Nicotine-induced EEG and behavioral arousal

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Review
Silvette. The actions of nicotine on central nervous system functions

PHILIP MORRIS TOBACCO COMPANY
Mangan. Relationships between photic driving, nicotine and memory

(One Philip Morris document explains why the company decided to conduct nicotine-related EEG research: "We are establishing an EEG laboratory in search of the reinforcing event. Brain waves are neuro-physiological phenomena, but they are legitimate subject matter for us in that brain events underlie behavioral events. Smoke-related changes in brain waves can give us clues as to smoke-related psychological changes." Philip Morris employee (almost certainly W.L. Dunn). *Smoker Psychology Program Review*. October 19, 1977. Page 9.)

R. J. REYNOLDS COMPANY

Gilbert. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie

Pritchard. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity

Pritchard. Electroencephalographic effects of cigarette smoking

Robinson. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine

BROWN AND WILLIAMSON TOBACCO CORPORATION, Unpublished
Brotzge. Human smoking studies: acute effect of cigarette smoke on brain wave alpha rhythm-first report

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Golding. Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving

Golding. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation

Golding. Effects of cigarette smoking on measures of arousal, response suppression, and excitation/inhibition balance

BRITISH-AMERICAN TOBACCO COMPANY, LTD, Unpublished
Comer. Interaction of smoke and the smoker. Part 3: The effect of cigarette smoking on the contingent negative variation

Wiley. Effects of nicotine on the central nervous system

INDUSTRY SUPPORTED AMA/ERF STUDIES
Murphree. Electroencephalographic changes in man following smoking

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat

Armitage. Pharmacological basis for the tobacco smoking habit

Ashton. The use of event-related slow potentials of the brain as a means to analyse the effects of cigarette smoking and nicotine in humans

Hall. Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb

OTHER

Edwards. Smoking, nicotine and electrocortical activity

Knott. Effects of cigarette smoking on subjective and brain evoked responses to electrical pain stimulation

Knott. Reaction time, noise distraction and autonomic responsivity in smokers and non-smokers

²⁵³ **INDUSTRY SUPPORTED AMA/ERF STUDIES**

Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

R. J. REYNOLDS COMPANY

Robinson. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Mangan. The effects of cigarette smoking on vigilance performance

Effects on performance and behavior. Industry-funded scientists have conducted research to characterize nicotine's effects on behavioral performance and cognitive function.²⁵⁴

COUNCIL FOR TOBACCO RESEARCH-USA

Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Marks. Genetics of nicotine response in four inbred strains of mice

Pradhan. Effects of nicotine on several schedules of behavior in rats

Yamamoto. Nicotine-induced EEG and behavioral arousal

TOBACCO RESEARCH COUNCIL LABS, U.K.

Warwick. Experimental studies of the behavioral effects of nicotine

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COUNCIL FOR TOBACCO RESEARCH-USA

Bhagat. Effect of nicotine on the swimming endurance of rats

Heinstra. The effects of deprivation of cigarette smoking on psychomotor performance

Levin. Memory enhancing effects of nicotine

Marks. Genetics of nicotine response in four inbred strains of mice

Nelsen. Chronic nicotine treatment in rats

Nelsen. Protection by nicotine from behavioral disruption caused by reticular formation stimulation in the rat

Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews

Essman. Drug effects and learning and memory processes

Silvette. The actions of nicotine on central nervous system functions

PHILIP MORRIS TOBACCO COMPANY

Colrain. Effects of post-learning smoking on memory consolidation.

DeNoble. Behavioral effects of intravenicularly administered (-)-nicotine on fixed ratio schedules of food presentation in rats

Mangan. Relationships between photic driving, nicotine and memory

Woodson. Effects of nicotine on the visual evoked response

R. J. REYNOLDS COMPANY

Fritchard. Enhancement of continuous performance task reaction time by smoking in non-deprived smokers

Fritchard. Electroencephalographic effects of cigarette smoking

BRITISH-AMERICAN TOBACCO COMPANY, LTD.

Mangan. The effects of cigarette smoking on vigilance performance

Mangan. The effects of smoking on memory consolidation

INDUSTRY SUPPORTED AMA/ERF STUDIES

Schechter. C.N.S. effect of nicotine as the discriminative stimulus for the rat in a T-maze

TOBACCO RESEARCH COUNCIL LABS, U.K.

Armitage. Pharmacological basis for the tobacco smoking habit

Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour

Morrison. Effects of nicotine on motor co-ordination and spontaneous activity in mice

Morrison. The effects of nicotine on punished behaviour

Warwick. Experimental studies of the behavioral effects of nicotine

Weanes. Effects of nicotine on stimulus sensitivity and response bias in a visual vigilance task

Weanes. The separate and combined effects of scopolamine and nicotine on human information processing

Weanes. Effects of scopolamine and nicotine on human rapid information processing performance

Weanes. Effects of smoking on rapid information processing performance

TOBACCO RESEARCH COUNCIL, UK, Literature Reviews

Hall. New evidence for a relationship between tobacco smoking, nicotine dependence, and stress

Weanes. Smoking, nicotine and human performance

OTHER

Anderson. Effects of cigarette smoking on incidental memory

Battig. The effect of pre- and post-trial application of nicotine on the 12 problems of the Hebb-Williams-test in the rat

Driscoll. Effects of nicotine on the shuttlebox behavior of trained guinea pigs

Hasenfratz. Action profiles of smoking and caffeine: Stoop effect, EEG, and peripheral physiology

Hasenfratz. Can smoking increase attention in rapid information processing during noise?

Knott. Reaction time, noise distraction and autonomic responsivity in smokers and non-smokers

Knott. Noise and task induced distraction effects on information processing: Sex differences in smokers and non-smokers

Nordberg. Effect of nicotine on passive avoidance behaviour and motoric activity in mice

Roth. Smoking deprivation in "early" and "late" smokers and memory functions

Neuroendocrine effects. Tobacco industry-supported studies have demonstrated that nicotine affects hormone secretion and several endocrine functions involved in modulation of mood and behavior. These studies showed that nicotine stimulates the secretion of corticosteroids and catecholamines and decreases the secretion of thyroid stimulating hormone, leutinizing hormone, and prolactin.²⁵⁵

2. Industry Research on Nicotine Delivery to the Blood and Brain

The tobacco industry has studied the bioavailability of nicotine in tobacco products and how nicotine is distributed throughout the body, after absorption into the bloodstream. This has led to the industry's development of sophisticated techniques for determining, quantitatively and qualitatively, the presence of nicotine and its metabolites in body fluids.²⁵⁶

Wesnes. The effects of cigarettes of varying yield on rapid information processing

²⁵⁵ COUNCIL FOR TOBACCO RESEARCH-USA

Andersson. Involvement of D1 dopamine receptors in the nicotine-induced neuro-endocrine effects and depletion of diencephalic catecholamine stores in the male rat

Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male rat

Andersson. Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohipophysial hormones

Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus

Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohipophysial hormones and corticosterone

Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat

Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohipophysial hormones in the male rat

Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications

Fuxe. Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro

Rubin. Nicotine-induced stimulation of steroidogenesis in adrenocortical cells of the cat

Siegel. Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relationship to neuroendocrine function

Westfall. Effect of 4,4'-biphenylenebis-[(2-oxoethylene)-bis-(2,2'-diethoxyethyl)] dimethylammonium dibromide (DMAE) on accumulation and nicotine-induced release of norepinephrine in the heart

Westfall. Specificity of blockade of the nicotine-induced release of 3H-norepinephrine from adrenergic neurons of the guinea-pig heart by various pharmacological agents

R. J. REYNOLDS COMPANY

Mitchell. Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain

TOBACCO RESEARCH COUNCIL LABS., U.K.

Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour

OTHER

Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor

²⁵⁶ AMERICAN TOBACCO COMPANY

Castro. Nicotine antibodies: comparison of ligand specificities of antibodies produced against two nicotine conjugates

COUNCIL FOR TOBACCO RESEARCH-USA

Castro. Nicotine enzyme immunoassay

Castro. Radioimmunoassays of drugs of abuse in humans: a review

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

McNiven. Determination of nicotine in smokers' urine by gas chromatography

Monji. Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay

R. J. REYNOLDS COMPANY

Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Nicotine pharmacokinetics. Numerous publications document the tobacco industry's involvement in investigating all aspects of the pharmacokinetics of nicotine. (Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of drugs in the body.) Areas that the industry has researched include:

- general pharmacokinetics of nicotine (absorption, distribution, metabolism, elimination);²⁵⁷

Davis. The determination of nicotine and cotinine in plasma

Kyerematen. Radiometric high performance liquid chromatographic assay for nicotine and twelve of its metabolites

Kyerematen. Pharmacokinetics of nicotine and 12 metabolites in the rat

Langone. Idiotype-anti-idiotypic hapten immunoassays: assay for cotinine

McManus. A new quantitative thermospray LC-MS method for nicotine and its metabolites in biological fluids

BRITISH-AMERICAN TOBACCO COMPANY, Unpublished
Backhurst. Further work on extractable nicotine

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

Read. Method for nicotine and cotinine in blood and urine

Read. Nicotine studies: A second report. Estimation of whole body nicotine dose by urinary nicotine and cotinine measurement

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Funded -- Battelle Unpublished Studies
Geissbuhler. The fate of nicotine in the body

Haselbach. A tentative hypothesis on nicotine addiction

TOBACCO RESEARCH COUNCIL I.A.R.S., U.K.

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anesthetized cats

Beckett. Analysis of nicotine-1-N-oxide in urine, in the presence of nicotine and cotinine, and its application to the study of *in vivo* nicotine metabolism in man

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Biber. Determination of nicotine and cotinine in human serum and urine: an interlaboratory study

Isaac. Cigarette smoking and plasma levels of nicotine

Schievelbein. Nicotine Workshop

Schmitterlow. Distribution of Nicotine in the Central Nervous System

Schmitterlow. Tissue distribution of C14-nicotine and Related Compounds

Szuts. Long-term fate of [¹⁴C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall

²⁵⁷ COUNCIL FOR TOBACCO RESEARCH-USA

Becker. Studies on nicotine absorption during pregnancy

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Hibberd. Enzymology of the metabolic pathway from nicotine to cotinine, *in vitro*

Kershbaum. Cigarette, cigar, and pipe smoking. Some differences in biochemical effects

Monji. Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay

Rama. Distribution and Retention of nicotine and its major metabolite cotinine in the rat as a function of time

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews

Larson. Tobacco -- Experimental and Clinical Studies

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement I

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement II

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement III

AMERICAN TOBACCO COMPANY

Haag. Studies on the fate of nicotine in the body I: The effect of pH on the urinary excretion of nicotine by tobacco smokers

Larson. Studies on the fate of nicotine in the body VI: Observations on the relative rate of elimination of nicotine by the dog, cat, rabbit and mouse

Larson. Studies on the fate of nicotine in the body II: On the fate of nicotine in the dog

Larson. Studies on the fate of nicotine in the body IV: Observations on the chemical structure of an end product of nicotine metabolism

McKennis. N-methylation of nicotine and cotinine *in vivo*

Owen. Studies on the fate of nicotine in the animal body. VIII: Observations on the number and chemical nature of nicotine metabolites in the dog and cat

Weatherby. Rate of elimination of nicotine by the rabbit

R. J. REYNOLDS COMPANY

Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Caldwell. Intra-gastric nitrosation of nicotine is not a significant contributor to nitrosamine exposure

deBethizy. Chemical and biological studies of a cigarette that heats rather than burns tobacco

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

- factors affecting the absorption of nicotine into the bloodstream, including route of administration;²⁵⁸
- distribution of nicotine to the brain;²⁵⁹ and

Hammond. Metabolism of nicotine by rat liver cytochromes P-450: Assessment utilizing monoclonal antibodies to nicotine and cotinine

Kyerematen. Pharmacokinetics of nicotine and 12 metabolites in the rat

Kyerematen. Disposition of nicotine and eight metabolites in smokers and nonsmokers: Identification in Smokers of two metabolites that are longer lived than cotinine

BROWN AND WILLIAMSON TOBACCO CORPORATION, Unpublished
Brötze. Human smoking studies: acute effect of cigarette smoke on brain wave alpha rhythm - first report

BRITISH-AMERICAN TOBACCO COMPANY, LTD., Funded -- Unpublished Battelle Studies
Geissbuhler. The fate of nicotine in the body

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption and metabolism of nicotine from cigarettes

Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Beckett. Effect of smoking on nicotine metabolism in vivo in man

Beckett. Analysis of nicotine-1-N-oxide in urine, in the presence of nicotine and cotinine, and its application to the study of in vivo nicotine metabolism in man

Beckett. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes

Jenner. Species variation in the metabolism of R-(+) and S-(-)nicotine by alpha-C- and N-oxidation in vitro

Jenner. Factors affecting the in vitro metabolism of R-(+) and S-(-)nicotine by guinea-pig liver preparations

OTHER
Cholerton. Sources of inter-individual variability in nicotine pharmacokinetics

Cohen. Monograph on the Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking

Hasenfratz. Development of central and peripheral smoking effects over time

Pilotti. Studies on the identification of tobacco alkaloids, their mammalian metabolites and related compounds by gas chromatography- mass spectrometry

Schievelbein. Nicotine Workshop

Schmitterlow. Tissue distribution of C14-nicotine

Schmitterlow. Distribution of nicotine in the central nervous system

Szuts. Long-term fate of [14C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall

²⁵⁸ **COUNCIL FOR TOBACCO RESEARCH-USA**
Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Kershbaum. Cigarette, cigar, and pipe smoking. Some differences in biochemical effects

R. J. REYNOLDS COMPANY
deBethizy. Chemical and biological studies of a cigarette that heats rather than burns tobacco

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Backhurst. Further Work on Extractable Nicotine

Evelyn. Retention of nicotine and phenols in the human mouth

Evelyn. Transfer of nicotine from smoke into blood using a perfused canine lung

Evelyn. Absorption of nicotine via the mouth: studies using animal models

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption of nicotine by man during cigar smoking [proceedings]

Armitage. Absorption of nicotine from small cigars

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

OTHER
Hasenfratz. Development of central and peripheral smoking effects over time

Schievelbein. Nicotine workshop: Absorption of nicotine under various conditions (an introductory review)

²⁵⁹ **COUNCIL FOR TOBACCO RESEARCH-USA**
Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Vineck. Synthesis of 4,4-ditritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Creighton. Relative contributions of nicotine and carbon monoxide to human physiological response

Creighton. Further studies on the effect of nicotine on human physiological response

- plasma profiles of nicotine and its metabolites.²⁶⁰

Nicotine metabolism. The industry has investigated the metabolic fate of nicotine, including the metabolites (breakdown products) of nicotine.²⁶¹ Studies have also been done on the enzymatic systems involved in nicotine

Isaac. The Absorption and Effects of Nicotine from Inhaled Tobacco Smoke

INDUSTRY SUPPORTED AMA/ERF STUDIES

Rosecrans. Brain area nicotine levels in male and female rats with different levels of spontaneous activity

Rosecrans. Brain area nicotine levels in male and female rats of two strains

OTHER

Cholerton. Sources of inter-individual variability in nicotine pharmacokinetics

Schmitterlow. Distribution of Nicotine in the Central Nervous System

OTHER, Literature Review

Edwards. Smoking, nicotine and electrocortical activity

²⁶⁰

COUNCIL FOR TOBACCO RESEARCH-USA

Castro. Nicotine enzyme immunoassay

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Monji. A Plasma nicotine pharmacokinetics in dogs after intravenous administration: Determination by radioimmunoassay

Rama. Distribution and Retention of nicotine and its major metabolite cotinine, in the rat as a function of time

AMERICAN TOBACCO COMPANY

Castro. Nicotine antibodies: comparison of ligand specificities of antibodies produced against two nicotine conjugates

R. J. REYNOLDS COMPANY

Davis. The determination of nicotine and cotinine in plasma

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

Kyerematen. Pharmacokinetics of nicotine and 12 metabolites in the rat Application of a new radiometric high performance liquid chromatography assay

Kyerematen. Radiometric high performance liquid chromatographic assay for nicotine and twelve of its metabolites

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

TOBACCO RESEARCH COUNCIL LABS, U.K.

Armitage. Absorption and metabolism of nicotine from cigarettes

Armitage. Absorption of nicotine by man during cigar smoking [proceedings]

Armitage. Absorption of nicotine from small cigars

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Stepney. Behavioural regulation of nicotine intake in cigarette smokers presented with a 'shortened' cigarette [proceedings]

OTHER

Isaac. Cigarette smoking and plasma levels of nicotine

Isaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smoke
Isaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smoke

Schievelbein. Nicotine Workshop

²⁶¹

COUNCIL FOR TOBACCO RESEARCH-USA

Aboud. Specific binding and metabolism of (-) and (+)-[3H]-nicotine in isolated rat hepatocytes and hepatocyte membranes

Hibberd. Nicotine delta 1' (5) iminium ion: a reactive intermediate in nicotine metabolism

Vineck. Synthesis of 4,4-ditritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer

AMERICAN TOBACCO COMPANY

Bowman. Studies on the metabolism of (-)-cotinine in the human

Bowman. Disposition and fate of (-)-cotinine-H3 in the mouse

Hucker. Studies on the metabolism of normicotine in the dog

Larson. Studies on the fate of nicotine in the body III: On the pharmacology of some methylated and demethylated derivatives of nicotine

Larson. Studies on the fate of nicotine in the body IV: Observations on the chemical structure of an end product of nicotine metabolism

McKennis. Gamma-(3-pyridyl)-gamma-methylaminobutyric acid as a urinary metabolite of nicotine

McKennis. The excretion and metabolism of nicotine

McKennis. Mammalian degradation of (-)-nicotine to 3-pyridylacetic acid and other compounds

McKennis. Demethylation in the metabolism of (-)-nicotine

McKennis. Metabolic release of methyl groups from a series of N-methylpyridinium compounds

McKennis. Metabolism of nicotine to (+)-gamma-(3-pyridyl)-gamma-methylaminobutyric acid

McKennis. Demethylation of cotinine in vivo

McKennis. Metabolites of nicotine and a synthesis of normicotine

metabolism.²⁶² Industry-supported research shows that smokers metabolize nicotine faster than non-smokers because one or more of the substances in cigarette smoke increases the production of the enzymes that metabolize nicotine.²⁶³ Industry-funded studies have also shown that there may be gender differences in the metabolism of nicotine.²⁶⁴

Nicotine pharmacodynamics. The tobacco industry has studied a wide range of factors related to the pharmacodynamics of nicotine and nicotine delivery systems. (Pharmacodynamics is the study of a drug's effects on the body over time. A pharmacodynamic study would involve, for example, administering a drug and then evaluating its behavioral and physiological effects over time.) The industry has funded research on:

- factors affecting the onset and duration of nicotine's physiological effects on the body;²⁶⁵

McKennis. Demethylation in the metabolism of (-)-nicotine in vivo

McKennis. N-methylation of nicotine and cotinine in vivo

McKennis. The Metabolic Formation of Gamma-(3-Pyridyl)-Gamma-Hydroxybutyric Acid and Its Possible Intermediary Role in the Mammalian Metabolism of Nicotine

McKennis. The isolation and structure of a ketoamide formed in the metabolism of nicotine

Meacham. Additional routes in the metabolism of nicotine to 3-pyridylacetate

Miller. Observations on the metabolism of nicotine by tissue slices

Owen. Studies on the fate of nicotine in the animal body VIII: Observations on the number and chemical nature of nicotine metabolites in the dog and cat

Schwartz. Studies on the degradation of the pyrrolidine ring of (-)-nicotine in vivo

Schwartz. Mammalian degradation of (-)-demethylcotinine

R. J. REYNOLDS COMPANY

Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Kyerematen. Disposition of nicotine and eight metabolites in smokers and nonsmokers: Identification in smokers of two metabolites that are longer lived than cotinine

TOBACCO RESEARCH COUNCIL LABS, U.K.

Jenner. Factors affecting the in vitro metabolism of R-(+) and S-(-)-nicotine by guinea-pig liver preparations

Jenner. Species variation in the metabolism of R-(+) and S-(-)-nicotine by alpha-C- and N-oxidation in vitro

OTHER

Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine

²⁶² **COUNCIL FOR TOBACCO RESEARCH-USA**

Hibberd. Enzymology of the metabolic pathway from nicotine to cotinine, in vitro

Wilson. Nicotine-like actions of cis-metanicotine and trans-metanicotine

R. J. REYNOLDS COMPANY

Hammond. Metabolism of nicotine by rat liver cytochromes P-450: Assessment utilizing monoclonal antibodies to nicotine and cotinine

²⁶³ **COUNCIL FOR TOBACCO RESEARCH-USA**

Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Jusko. Role of tobacco smoking in pharmacokinetics

TOBACCO RESEARCH COUNCIL LABS, U.K.

Beckett. The effect of smoking on nicotine metabolism in vivo in man

²⁶⁴ **COUNCIL FOR TOBACCO RESEARCH-USA**

Jusko. Role of tobacco smoking in pharmacokinetics

TOBACCO RESEARCH COUNCIL LABS, U.K.

Beckett. The effect of smoking on nicotine metabolism in vivo in man

OTHER

Cohen. Monograph on the Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking

²⁶⁵ **COUNCIL FOR TOBACCO RESEARCH-USA**

Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Hoff. Neurophysiological aspects of the action of nicotine

Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance

Sitzer. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists

TOBACCO RESEARCH COUNCIL LABS, U.K.

Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

- the relationship of nicotine's physiological effects on the body to nicotine blood levels;²⁶⁶ and
 - physiological effects of nicotine on the brain and their time-course.²⁶⁷
3. **Industry Research Establishes That Nicotine Produces Pharmacological Effects Similar to Those of Other Addictive Drugs**

The tobacco industry has conducted or sponsored studies which demonstrate that nicotine produces pharmacological effects similar to those of other addictive substances. See FINDINGS § I.B., *supra*, for a discussion of the properties of addictive substances. Indeed, a number of industry-funded studies state that

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement I

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement II

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement III

OTHER

Batig. Smoke yield of cigarettes and puffing behavior in men and women

Nordberg. Pharmacodynamic effects of nicotine and acetylcholine biosynthesis in mouse brain

²⁶⁶ **COUNCIL FOR TOBACCO RESEARCH-USA**

Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Westfall. Influence of nicotine on catecholamine metabolism in the rat

R.J. REYNOLDS COMPANY

Pritchard. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

OTHER

Isaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smoke

²⁶⁷ **COUNCIL FOR TOBACCO RESEARCH-USA**

Aboud. Comparison of the binding of optically pure (-) and (+)-[3H]nicotine to rat brain membranes

Anderson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male

Anderson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenoipophysal hormones and corticosterone

Bhagat. Influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat brain

Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids

Wong. Pharmacology of nicotinic receptor-mediated inhibition in rat dorsolateral septal neurones

Yamamoto. Nicotine-induced EEG and behavioral arousal

R.J. REYNOLDS COMPANY

Byrd. Evidence for urinary excretion of glucuronide conjugates of nicotine, cotinine, and trans-3'-hydroxycotinine in smokers

INDUSTRY SUPPORTED SYMPOSIA

Binnie. The effect of cigarette smoking on the contingent negative variation (CNV) and eye movement

INDUSTRY SUPPORTED AMA/ERF STUDIES

Hirschhorn. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine

Rosecrans. Brain area nicotine levels in male and female rats with different levels of spontaneous activity

TOBACCO RESEARCH COUNCIL LABS, U.K.

Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat

Wesnes. Smoking, nicotine and human performance

OTHER

Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine neurons

Hasenfratz. Development of central and peripheral smoking effects over time

Hasenfratz. Can smoking increase attention in rapid information processing during noise? Electrocortical, physiological and behavioral effects

Perez de la Mora. Neurochemical effects of nicotine on glutamate and GABA mechanisms in the rat brain

OTHER, Literature Review

Edwards. Smoking, nicotine and electrocortical activity

nicotine is an addictive/dependence-producing drug.²⁶⁸

Nicotine psychoactivity and discrimination studies. Industry studies have shown that nicotine is psychoactive and produces clearly discriminable stimulus effects²⁶⁹ in both animals and humans.²⁷⁰

Nicotine reinforcement/self-administration studies. The industry has examined nicotine's ability to serve as a positive reinforcer in self-administration studies involving rats and monkeys. For example, Philip Morris conducted studies in rats demonstrating that nicotine is self-administered by rats and has other hallmark properties of addictive substances.²⁷¹ The industry-supported research on monkeys led prominent drug addiction researchers Deneau and Inoki to conclude in a paper published in 1967 that nicotine "may be one of

²⁶⁸ **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
 Bosse. Age and addiction to smoking

Martin. Tobacco Smoking and Nicotine: A Neurobiological Approach

Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence

Rosecrans. Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms

Svensson. Effect of nicotine on dynamic function of brain catecholamine neurons

Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids

Williams. Stability of a factor-analytic description of smoking behavior

TOBACCO RESEARCH COUNCIL LABS, U.K.

Hall. New evidence for a relationship between tobacco smoking, nicotine dependence, and stress

OTHER

Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine-induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems

Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area

²⁶⁹ These effects are evaluated in animals using drug discrimination techniques which enable direct comparisons of the effects of different drugs. Such studies evaluate whether an animal experiences a psychoactive effect from a drug and facilitate comparisons of the effect of the study drug with the effect of other psychoactive drugs. Industry-funded studies have shown that animals can distinguish (discriminate) nicotine from other drugs or a placebo, and can communicate their identification of nicotine (as distinct from other drugs) to the investigator by pressing a bar or providing other behavioral signals. These studies also provide information on the similarity of nicotine's effects to effects of other dependence-producing drugs, including the degree to which nicotine mimics the psychoactive effects of those other drugs. See p. 95.

²⁷⁰ **INDUSTRY SUPPORTED AMA/ERF STUDIES**

Hirschhorn. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine

Schechter. Behavioral evidence for two types of cholinergic receptors in the C.N.S.

Schechter. Behavioral tolerance to an effect of nicotine in the rat

Schechter. Effect of mecamylamine on discrimination between nicotine- and arecoline- produced cues

Schechter. Nicotine as a discriminative cue in rats: inability of related drugs to produce a nicotine-like cueing effect

Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine

Schechter. C.N.S. effect of nicotine as the discriminative stimulus for the rat in a T-maze

COUNCIL FOR TOBACCO RESEARCH-U.S.A

Chance. A comparison of nicotine and structurally related compounds as discriminative stimuli

Rosecrans. Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms

PHILIP MORRIS TOBACCO COMPANY

Kallman. Nicotine as a discriminative stimulus in human subjects

TOBACCO RESEARCH COUNCIL LABS, U.K.

Morrison. Nicotine injections as the conditioned stimulus in discrimination learning

²⁷¹ **PHILIP MORRIS TOBACCO COMPANY, Unpublished**

DeNoble. Manuscript: Nicotine as a Positive Reinforcer for Rats: Effects of Infusion Dose and Fixed Ratio Size

See also pp. 278-79, *infra*.

INDUSTRY SUPPORTED AMA/ERF STUDIES

Deneau. Nicotine self-administration in monkeys

the substances in tobacco smoke which is responsible for man's use of tobacco."²⁷² The industry has also funded studies demonstrating that nicotine could enhance the rewarding effects of electrical brain stimulation.²⁷³ A book resulting from The International Smoking Behaviour Conference held at Chelwood Vachery, Sussex, England, in 1978, which was edited by a senior scientist at British-American Tobacco, included a "Conference Overview" stating: "At this stage, we hypothesize that nicotine (possible [sic] interacting with tar) is the main reinforcing agent in cigarettes . . ." ²⁷⁴ Moreover, as noted earlier, the industry has conducted studies showing that nicotine is active in the same dopaminergic pathways that modulate cocaine's effects. These studies are relevant to understanding how nicotine causes addiction.

Tolerance to nicotine. Tolerance to the physiological and behavioral effects of nicotine has been thoroughly studied by the tobacco industry and has been demonstrated to occur in animals as a result of nicotine use.²⁷⁵

²⁷² **INDUSTRY SUPPORTED AMA/ERF STUDIES**
Deneau. Nicotine self-administration in monkeys

²⁷³ **COUNCIL FOR TOBACCO RESEARCH-U.S.A.**
Olds. Comparison of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior
Pradan. Effects of nicotine on self-stimulation in rats

²⁷⁴ **INDUSTRY SUPPORTED SYMPOSIA**
Jarvik. Smoking Behaviour -- Physiological and psychological influences. 31. Conference overview

²⁷⁵ **COUNCIL FOR TOBACCO RESEARCH-U.S.A.**
Abood. Acute and chronic effects of nicotine in rats and evidence for a non-cholinergic site of action
Abood. Behavioral and biochemical studies in rats after chronic exposure to nicotine
Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male
Cronan. Effects of chronically administered nicotine and saline on motor activity in rats
Domino. Tolerance to the effects of daily nicotine on rat bar pressing behavior for water reinforcement
Fuxe. Effects of nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain
Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance
Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats
Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence
Stitzer. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists
Wenzel. Studies on the acute and chronic depressor actions of nicotine in the rat
Westfall. Studies on the mechanism of tolerance to nicotine-induced elevations of urinary catecholamines
R. J. REYNOLDS COMPANY
Bjercke. Anti-idiotypic antibody probes of neuronal nicotinic receptors
Collins. Modulation of nicotinic receptors by chronic exposure to nicotinic agonists and antagonists
Marks. Downregulation of nicotinic receptor function after chronic nicotine infusion

PHILIP MORRIS TOBACCO COMPANY, Unpublished
DeNoble. Manuscript: Development of behavioral tolerance following chronic nicotine administration.

INDUSTRY SUPPORTED AMA/ERF STUDIES
Schechter. Behavioral tolerance to an effect of nicotine in the rat

TOBACCO RESEARCH COUNCIL LABS., U.K.
Morrison. The occurrence of tolerance to a central depressant effect of nicotine

OTHER
Larsson. Subchronic treatment of rats with nicotine: effects on tolerance and on [3H]acetylcholine and [3H]nicotine binding in the brain

Nordberg. Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs

Nordberg. Effect of long-term nicotine treatment on [3H]nicotine binding sites in the rats brain

Nicotine's withdrawal effects. Scientists funded by the tobacco industry have conducted research on various aspects of withdrawal, including potential neurochemical mechanisms²⁷⁶ and the effects of withdrawal on performance.²⁷⁷ Symptoms of withdrawal may include craving, irritability, nervousness, tension, emotional strain, depression, inability to concentrate, sleep disturbance, sweating, gastrointestinal changes, drop in blood pressure and pulse rate, impaired performance, and changes in the electroencephalogram.²⁷⁸

The industry has also funded studies showing that tobacco users report "craving" for tobacco.²⁷⁹

Continued use of tobacco despite attempts to quit. As described in § II.C.4., *infra*, the tobacco industry has conducted a number of studies documenting the large percentage of tobacco users who have attempted to quit using tobacco and the very small percentage who have succeeded.

²⁷⁶ COUNCIL FOR TOBACCO RESEARCH-U.S.A.

Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence

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Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement II

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement III

AMERICAN TOBACCO COMPANY

Finnegan. The role of nicotine in the cigarette habit

²⁷⁷ COUNCIL FOR TOBACCO RESEARCH-U.S.A.

Heimstra. The effects of deprivation of cigarette smoking on psychomotor performance

Heimstra. Effects of smoking upon sustained performance in a simulated driving task

COUNCIL FOR TOBACCO RESEARCH-U.S.A., Literature Reviews

Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement III

OTHER

Hasenfratz. Psychophysiological reactions during active and passive stress coping following smoking cessation

²⁷⁸ COUNCIL FOR TOBACCO RESEARCH-U.S.A., Literature Reviews

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement II

Larson. Tobacco – Experimental and Clinical Studies – A Comprehensive Account of the World Literature – Supplement III

AMERICAN TOBACCO COMPANY

Finnegan. The role of nicotine in the cigarette habit

²⁷⁹ R. J. REYNOLDS COMPANY

Robinson. The meaning of addiction: reply to West

OTHER

Hasenfratz. Development of central and peripheral smoking effects over time

Hasenfratz. Post-hunch smoking for pleasure seeking or arousal maintenance?