**DATE OF PREPARATION:** 22 Oct 2018
**CHEMICAL NAME:** Nicotine
**CAS:** 54-11-5

REPORT TITLE: Existence of any studies relating to the carcinogenicity, mutagenicity or toxicity for reproduction of the ingredient

| KEYWORD | STUDIES |
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| mutagenicity | TITLE:<br>Genotoxicity of nicotine and cotinine in the bacterial luminescence test.<br><br>ABSTRACT:<br>Cotinine was positive in the absence of S9 in the bacterial luminescence genotoxicity test at 1.25 mg/ml (9-15 h incubation) and at 2.50 mg/ml (18-30 incubation hours) signifying potential mutagenicity and teratogenicity. In the presence of S9, cotinine was positive at 1.25 mg/ml after 9 incubation hours. In contrast, nicotine was not at any concentration or incubation time. Nicotine/cotinine mixtures were still positive at physiological concentrations, with potentiation relative to cotinine alone with and without S9. Standard additions of nicotine to other positive controls such as 2-aminoanthracene (2AA) (a mutagen causing point mutations on activation), phenol (a DNA intercalator), and N-methyl-N'-nitrosoguanidine (MNNG) (a direct-acting point mutagen) revealed a complex nicotine effect. Nicotine antagonized MNNG without S9, and potentiated MNNG with S9, 2AA with and without S9, and phenol without S9. Cotinine was not a very potent agent relative to the positive controls. Since cotinine has been considered an inactive biological monitoring marker of nicotine absorption in humans, the present results indicate that the many health effect correlations based on cotinine in urine, serum, saliva, and blood may involve more cause and effect than thought hitherto.<br><br>SOURCE:<br>*Mutat Res 1995 Dec;335(3):275-83* |
| reproductive effects | TITLE:<br>Nicotine and its influence on the female reproductive system.<br><br>ABSTRACT:<br>This brief review focuses on women and how their smoking can influence physiologic events from ovulation to birth, specifically the effects of nicotine, since effects of carbon monoxide in pregnancy have been reviewed extensively elsewhere. The nicotine alkaloid, which enters the body as a gas, has easy access to the brain stem and the central nervous system of the smoker, and it exerts effects on the nervous systems by activating nicotine cholinergic receptor sites. This interaction with the nervous systems has the consequence of altering adenohypophysial, neurohypophysial, adrenal, and catecholamine secretion patterns. These endocrine responses affect the continuum of events from ovulation to birth in the following ways: 1) alteration of H-P-O axis activity affecting ovulation or early tropic support preceding placental function; 2) alterations in oviductal or uterotubal junction activity leading to inappropriate entry of the blastocyst into the uterus; 3) alteration of catecholamine mediated changes in uterine or placental blood |

flow patterns; 4) fetal hypoxic episodes occurring in response to HbCO accumulation; and 5) inappropriate changes in fetal endocrine function.

SOURCE:
*J Reprod Med. 1980, Nov; 25(5):243-50. [The Journal of reproductive medicine]*

carcinogenic

TITLE:
Electronic cigarettes are a source of thirdhand exposure to nicotine.

ABSTRACT:
INTRODUCTION: Substances remaining on the surfaces in areas where people have smoked contribute to thirdhand exposure. Nicotine from tobacco smoke has been shown to react with oxidizing chemicals in the air to form secondary pollutants, such as carcinogenic nitrosamines. While previous studies have demonstrated thirdhand exposure to nicotine from tobacco smoke, none have investigated whether nicotine from electronic cigarettes (e-cigarettes) can also be deposited on various surfaces.
METHODS: Three brands of e-cigarettes were refilled with varying nicotine concentrations. We released 100 puffs from each product directly into an exposure chamber. Surface wipe samples were taken from 5 indoor 100 cm(2) surfaces (window, walls, floor, wood, and metal) pre- and post-release of vapors. Nicotine was extracted from the wipes and was analyzed using gas chromatography. RESULTS: Three of the 4 experiments showed significant increases in the amount of nicotine on all five surfaces. The floor and glass windows had the greatest increases in nicotine, on average by a factor of 47 and 6, respectively (p
SOURCE:
*Nicotine Tob Res. 2015, Feb; 17(2):256-8. [Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco]*

genotoxicity

TITLE:
The tobacco alkaloid nicotine demonstrates genotoxicity in human tonsillar tissue and lymphocytes.

ABSTRACT:
Recent studies suggest a direct contribution of nicotine, the addictive component of tobacco and tobacco smoke, to human carcinogenesis. To assess the genotoxicity of nicotine, the DNA-damaging effect on human lymphocytes and target cells from lymphatic tissue of the palatine tonsils from 10 healthy patients was tested with the alkaline single-cell microgel electrophoresis (Comet) assay. The degree of DNA migration, a measure of possible DNA single strand breaks, alkali labile sites, and incomplete excision repair sites, was expressed as the Olive tail moment, the percentage of DNA in the tail, and the tail length. One hour exposure to nicotine at 0.125, 0.25, 0.5, 1, 2, and 4 mM induced a statistically significant dose-dependent increase of DNA migration up to 3.8-fold and 3.2-fold in tonsillar cells and lymphocytes, respectively. The lowest concentration eliciting significant DNA damage was 0.5 mM nicotine. The genotoxic effect was confirmed in a second series of experiments using nicotine of high purity from two different suppliers. There were no significant differences between the two series, excluding artifacts from the source of nicotine. Finally, DNA damage by nicotine was compared in cells incubated in medium strictly adjusted to neutral pH, with non-adjusted medium becoming alkaline with increasing nicotine concentrations. Again no differences in DNA migration were observed. The data indicate that nicotine expresses significant direct genotoxic effects in human target cells in vitro. However, no differences in DNA damage were observed in cells from smokers and nonsmokers incubated without nicotine. The lack of higher DNA damage in smokers compared to nonsmokers could be a question of nicotine dose, rapid DNA repair, or interactions with other smoke constituents. These results require further investigations on the contribution of nicotine to tobacco carcinogenesis.

SOURCE:
*Toxicol Sci. 2005, Aug; 86(2):309-17. [Toxicological sciences : an official journal of the Society of Toxicology]*

mutagenicity

HUMAN EXPOSURE STUDIES

Prior to each exptl session, three male smokers were administered varying amounts of

nicotine via either chewing nicotine gum or smoking low or high nicotine yield cigarettes. During the 60 min prior to some of the sessions, subjects were given 4 pieces of nicotine gum to chew. Each piece was either placebo or contained 2 mg of nicotine (doses were 0, 2, 4 or 8 mg nicotine total). They were then exposed to a free operant avoidance schedule in which a lever press postponed a point subtraction on a counter for 20 sec (points exchangeable for money). Subtractions were scheduled to occur every 5 sec in the absence of lever presses. Subjects participated daily in 30 min exptl sessions, Mon through Fri (from 106 to 151 total sessions). Blood samples were obtained just prior to nicotine treatment, immediately following the treatment, and 30 min later on particular days. Smoking cigarettes resulted in increased avoidance responding relative to baseline nonsmoking rates. Smoking the low nicotine delivery cigarettes produced increased avoidance responding in 2 of the 3 subjects; high nicotine delivery cigarettes increased avoidance in all subjects (p/HUMAN EXPOSURE STUDIES/ 40 smokers and 40 nonsmokers were matched for age and gender. Smokers either smoked a high nicotine (0.77 mg nicotine) or low nicotine (0.13 mg) cigarette, while nonsmokers sham smoked. Twelve min after smoking, participants viewed a stress inducing movie. Smoking higher nicotine delivery cigarettes during the movie, as compared to smoking for low nicotine control cigarettes, was associated with reductions in anxiety (p/HUMAN EXPOSURE STUDIES/ Systemic effects of nicotine exposure were studied in eight healthy male cigarette smokers (ages 27 to 61 yr; mean, 49 yr) during free use of oral snuff, chewing tobacco, and cigarettes. Participants used either one of the above 3 substances or abstained from all tobacco during four 3 or 4 day blocks. Concentrations of nicotine and cotinine, cardiovascular effects, and urine sodium, catecholamines and mutagenicity were measured over 24 hr at the end of each treatment block. Mutagenic activity of the urine was measured by the Salmonella-histidine auxotrophic-reversion assay. Circadian exposure to nicotine and cardiovascular effects, including urinary catecholamine excretion, were similar for all forms of tobacco use. Urine sodium excretion was greater while using smokeless tobacco than while smoking. Urine mutagenicity was markedly increased while smoking cigarettes and tended to be increased while chewing tobacco but not while using oral snuff.

SPURCE: *Benowitz NL et al; Ann Intern Med 111 (2): 112-6 (1989)*

mutagenicity — GENOTOXICITY

Level of urinary nicotine were measured in 21 non-smokers, 26 smokers of blond tobacco, 9 smokers of black tobacco and 5 smokers of both types, all eating a similar diet. Two 24 hr samples from the subjects were collected over a 3 day period. Statistically significant positive dose-effect relationships were obtained between the urinary nicotine + cotinine levels and the number of revertants (Salmonella typhimurium TA 98, with a metabolic activation system. A linear dose-effect relationship between urinary mutagenicity (ie log revertants of S typhimurium TA98) and nicotine + cotinine levels or number of cigarettes per day, was established for smokers of blond tobacco.

*SOURCE: Malaveille C et al; Carcinogenesis 10 (3): 577-86 (1989)*

mutagenicity — GENOTOXICITY

Smoke condensates prepared from blond and black Italian cigarettes were tested in S typhimurium TA98 and in E coli PQ37 using liquid incubation procedures. Plate incorporation assays with Salmonella were also performed. Cigarette smoke condensate from blond tobacco contained 37 ug nicotine/mg cigarette smoke condensate, while that of black tobacco contained 67 ug. Smoke condensate of black tobacco was 1.2 to 1.4 times more mutagenic than that of blond tobacco when activity is expressed per mg cigarette smoke condensate. The order was reversed when mutagenicity was expressed per ug nicotine, as black tobacco cigarette smoke condensate contained 1.8 times more nicotine than blond cigarette smoke condensate. Liquid incubation assays revealed a 12- to 14-fold higher mutagenicity than plate incorporation. Both cigarette smoke condensates were found to be directly active in inducing DNA repair functions.

*Malaveille C et al; Carcinogenesis 10 (3): 577-86 (1989)*

genotoxicity — GENOTOXICITY

... Nicotine has induced repairable DNA damage in an E. coli test system and demonstrated genotoxicity in Chinese hamster ovary cells.

*SOURCE: American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)*

carcinogen

TITLE:
Exposure to nicotine and a tobacco-specific carcinogen increase with duration of use of smokeless tobacco.

ABSTRACT:
BACKGROUND: Smokeless tobacco is an efficient delivery vehicle for nicotine and can contain significant amounts of carcinogens. However, few studies have examined factors that might moderate levels of nicotine or carcinogen exposure. AIMS: To determine the effect of duration of smokeless tobacco use on the uptake of nicotine and a tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). METHODS: Questionnaires on use of smokeless tobacco were administered, and urine samples from 212 smokeless tobacco users were analysed for biomarkers of uptake of nicotine and NNK. The biomarkers were cotinine and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Male smokeless tobacco users were recruited for studies designed to investigate methods of reducing smokeless tobacco use. The questionnaire and biomarker data were obtained at baseline, prior to reduction. RESULTS: Levels of cotinine ($p < 0.001$) and total NNAL ($p < 0.001$) were significantly correlated with duration (in years) of use of smokeless tobacco products. Median cotinine and total NNAL were 2.4 and 2.1 times higher, respectively, in the > or = 21 years of use than in the 0-5 years of use category. CONCLUSIONS: Smokeless tobacco users adjust their intensity of use with experience in order to increase their nicotine dose, resulting in a corresponding increase in exposure to NNK, a powerful carcinogen. These results indicate the importance of educating smokeless tobacco users about the effects of prolonged use of these products.

SOURCE:
*Tob Control. 2008, Apr; 17(2):128-31. [Tobacco control]*

carcinogenic

TITLE:
Electronic cigarettes are a source of thirdhand exposure to nicotine.

ABSTRACT:
INTRODUCTION: Substances remaining on the surfaces in areas where people have smoked contribute to thirdhand exposure. Nicotine from tobacco smoke has been shown to react with oxidizing chemicals in the air to form secondary pollutants, such as carcinogenic nitrosamines. While previous studies have demonstrated thirdhand exposure to nicotine from tobacco smoke, none have investigated whether nicotine from electronic cigarettes (e-cigarettes) can also be deposited on various surfaces. METHODS: Three brands of e-cigarettes were refilled with varying nicotine concentrations. We released 100 puffs from each product directly into an exposure chamber. Surface wipe samples were taken from 5 indoor 100 cm(2) surfaces (window, walls, floor, wood, and metal) pre- and post-release of vapors. Nicotine was extracted from the wipes and was analyzed using gas chromatography. RESULTS: Three of the 4 experiments showed significant increases in the amount of nicotine on all five surfaces. The floor and glass windows had the greatest increases in nicotine, on average by a factor of 47 and 6, respectively ($p < .05$). The average amount of nicotine deposited on a floor during each experiment was 205 ?g/m(2) and varied from limit of quantitation to 550 ?g/m(2). CONCLUSIONS: This study indicates that there is a risk for thirdhand exposure to nicotine from e-cigarettes. Thirdhand exposure levels differ depending on the surface and the e-cigarette brand. Future research should explore the potential risks of thirdhand exposure to carcinogens formed from the nicotine that is released from e-cigarettes.

SOURCE:
*Nicotine Tob Res. 2015, Feb; 17(2):256-8. [Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco]*

mutagenic

GENOTOXICITY

In studies with Saccharomyces cerevisiae, nicotine was ... mutagenic at 100 ppm. In ... Salmonella typhimurium, TA 98 with metabolic activation, nicotine was not important in contributing to mutagenic potency of smoke condensate. Using mammalian cell culture system (hamster lung), concentration of nicotine in cigarette smoke had no influence on occurrence of atypical growth or malignant transformation.

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| | *SOURCE: Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V4:1230* |
| carcinogen | Using sidestream/mainstream ratios of nicotine and assuming a 10 L/min respiratory rate, the recent Surgeon General's Report estimates that from 0.6 to 30 ug of nicotine is inhaled in one hour by passive smoking(1). As a result of all-day monitoring, it was found that the highest amount of nicotine inhaled in a day was estimated to be up to 310 ug, equivalent to actively smoking 0.31 ordinary cigarettes(2). |
| | *SOURCE: (1) Guerin MR, Buchanan MV; Environmental Exposure to N-Aryl Compounds. Carcinog Mutagen Respons Aromat Amines Nitroarenes, Proc Int Conf Carcinogens. 3rd. pp. 37-45 (1988) (2) Muramatsu M et al; Int Arch Occup Environ Health 59: 545-50 (1987)* |
| carcinogen | Chronic Exposure or Carcinogenicity/... In dogs, daily sc injections ... for 18 months caused atrophy of retina, disorganization of layers, and reduction of number of cells. Changes in blood vessels were thought to be primarily responsible. |
| | *SOURCE: Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 747* |
| carcinogen | Level of urinary nicotine were measured in 21 non-smokers, 26 smokers of blond tobacco, 9 smokers of black tobacco, and 5 smokers of both types, all eating a similar diet. Two 24-hr samples from the subjects were collected over a 3-day period. The sum of urinary nicotine and cotinine levels was used as a measure of exposure to the number of cigarettes smoked. The nicotine + cotinine content in 24 hr urine was 0, 0 to 0.5, 0.5 to 1.5, 1.5 to 2.5, and >2.5 umol/mmol creatinine for subjects who smoked a average of 0.47, 3.56, 14.3, 18.9, and 19.8 cigarettes in 24 hr, respectively. |
| | *SOURCE: Malaveille C et al; Carcinogenesis 10 (3): 577-86 (1989)* |
| genotoxicity | ...Nicotine inhibited cell proliferation in mammalian cell cultures of human promyelocytic leukemic cells... |
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| genotoxicity | Injection of 0.07-0.09 mg nicotine into mice resulted in gross chromosomal aberrations in bone marrow cells. |
| | *SOURCE: BISHUN NP ET AL; ACTA BIOL (BUDAPEST) 23 (2): 175-80 (1972)* |
| mutagenicity | TITLE:<br>Genotoxicity of nicotine and cotinine in the bacterial luminescence test.<br><br>ABSTRACT:<br>Cotinine was positive in the absence of S9 in the bacterial luminescence genotoxicity test at 1.25 mg/ml (9-15 h incubation) and at 2.50 mg/ml (18-30 incubation hours) signifying potential mutagenicity and teratogenicity. In the presence of S9, cotinine was positive at 1.25 mg/ml after 9 incubation hours. In contrast, nicotine was not at any concentration or incubation time. Nicotine/cotinine mixtures were still positive at physiological concentrations, with potentiation relative to cotinine alone with and without S9. Standard additions of nicotine to other positive controls such as 2-aminoanthracene (2AA) (a mutagen causing point mutations on activation), phenol (a DNA intercalator), and N-methyl-N'-nitrosoguanidine (MNNG) (a direct-acting point mutagen) revealed a complex nicotine effect. Nicotine antagonized MNNG without S9, and potentiated MNNG with S9, 2AA with and without S9, and phenol without S9. Cotinine was not a very potent agent relative to the positive controls. Since cotinine has been considered an inactive biological monitoring marker of nicotine absorption in humans, the present results indicate that the many health effect correlations based on cotinine in urine, serum, saliva, and blood may involve more cause and effect than thought hitherto. TAXONOMIC NAME: VIBRIO FISCHERI TEST OBJECT: BACTERIA CONTROL: SOLVENT ASSAY: MISCELLANEOUS CATEGORY GENE MUTATIONS MEDICAL SUBJECT HEADINGS (MESH): Biotransformation Cotinine/METABOLISM Cotinine/*TOXICITY DNA/*DRUG EFFECTS Luminescence Mutagenicity Tests/*METHODS Mutagens/METABOLISM Mutagens/*TOXICITY Nicotine/METABOLISM Nicotine/*TOXICITY Support, Non-U.S. Gov't Tobacco Use Disorder/ETIOLOGY Vibrio/*DRUG EFFECTS Vibrio/*GENETICS |

SOURCE:
*Mutat Res 1995 Dec;335(3):275-83*

reproductive effects

TITLE:
Nicotine and its influence on the female reproductive system.

ABSTRACT:
This brief review focuses on women and how their smoking can influence physiologic events from ovulation to birth, specifically the effects of nicotine, since effects of carbon monoxide in pregnancy have been reviewed extensively elsewhere. The nicotine alkaloid, which enters the body as a gas, has easy access to the brain stem and the central nervous system of the smoker, and it exerts effects on the nervous systems by activating nicotine cholinergic receptor sites. This interaction with the nervous systems has the consequence of altering adenohypophysial, neurohypophysial, adrenal, and catecholamine secretion patterns. These endocrine responses affect the continuum of events from ovulation to birth in the following ways: 1) alteration of H-P-O axis activity affecting ovulation or early tropic support preceding placental function; 2) alterations in oviductal or uterotubal junction activity leading to inappropriate entry of the blastocyst into the uterus; 3) alteration of catecholamine mediated changes in uterine or placental blood flow patterns; 4) fetal hypoxic episodes occurring in response to HbCO accumulation; and 5) inappropriate changes in fetal endocrine function.

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genotoxicity

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Genotoxicity of nicotine and cotinine in the bacterial luminescence test.

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Cotinine was positive in the absence of S9 in the bacterial luminescence genotoxicity test at 1.25 mg/ml (9-15 h incubation) and at 2.50 mg/ml (18-30 incubation hours) signifying potential mutagenicity and teratogenicity. In the presence of S9, cotinine was positive at 1.25 mg/ml after 9 incubation hours. In contrast, nicotine was not at any concentration or incubation time. Nicotine/cotinine mixtures were still positive at physiological concentrations, with potentiation relative to cotinine alone with and without S9. Standard additions of nicotine to other positive controls such as 2-aminoanthracene (2AA) (a mutagen causing point mutations on activation), phenol (a DNA intercalator), and N-methyl-N'-nitrosoguanidine (MNNG) (a direct-acting point mutagen) revealed a complex nicotine effect. Nicotine antagonized MNNG without S9, and potentiated MNNG with S9, 2AA with and without S9, and phenol without S9. Cotinine was not a very potent agent relative to the positive controls. Since cotinine has been considered an inactive biological monitoring marker of nicotine absorption in humans, the present results indicate that the many health effect correlations based on cotinine in urine, serum, saliva, and blood may involve more cause and effect than thought hitherto.

SOURCE:
*Mutat Res. 1995, Dec; 335(3):275-83. [Mutation research]*

mutagenicity

HUMAN EXPOSURE STUDIES

Prior to each exptl session, three male smokers were administered varying amounts of nicotine via either chewing nicotine gum or smoking low or high nicotine yield cigarettes. During the 60 min prior to some of the sessions, subjects were given 4 pieces of nicotine gum to chew. Each piece was either placebo or contained 2 mg of nicotine (doses were 0, 2, 4 or 8 mg nicotine total). They were then exposed to a free operant avoidance schedule in which a lever press postponed a point subtraction on a counter for 20 sec (points exchangeable for money). Subtractions were scheduled to occur every 5 sec in the absence of lever presses. Subjects participated daily in 30 min exptl sessions, Mon through Fri (from 106 to 151 total sessions). Blood samples were obtained just prior to nicotine treatment, immediately following the treatment, and 30 min later on particular days. Smoking cigarettes resulted in increased avoidance responding relative to baseline nonsmoking rates. Smoking the low nicotine delivery cigarettes produced increased avoidance responding in 2 of the 3 subjects; high nicotine delivery cigarettes increased

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| mutagenicity | GENOTOXICITY |
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| carcinogen | LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity |
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| genotoxicity | GENOTOXICITY |

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| | *SOURCE: BISHUN NP ET AL; ACTA BIOL (BUDAPEST) 23 (2): 175-80 (1972)* |

The following information was generated from the Toxicology Bibliographic Information (TOXLINE, DART, HSDB, CRIS, GENETOX, IRIS, ITER, LACTMED, CHEMID, CPDB, CTD, HAZMAP, HPD, TOXMAP, TRI2014), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) on 2018-10-22

**DATE OF PREPARATION:** 22 Oct 2018
**CHEMICAL NAME:** Nicotine
**CAS:** 54-11-5

REPORT TITLE: Existence of an analysis of the possible addictive properties of the ingredient

| KEYWORD | STUDIES |
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| addiction | Toxicity and addiction are possible with the use of nicotine from any source. Sustained use of nicotine polacrilex preparations or transdermal or orally inhaled nicotine should not be encouraged because chronic consumption of nicotine may result in intoxication and dependence (addiction). In deciding whether to initiate therapy with nicotine polacrilex preparations or transdermal or orally inhaled nicotine, regardless of the presence of disease or pregnancy, the risk of nicotine replacement in a smoking-cessation program should be weighed against the hazard of continued smoking concurrent with nicotine-replacement therapy and the likelihood of achieving smoking cessation without such pharmacologic management.<br><br>SOURCE: *American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)*] |
| addiction | Toxicity and addiction are possible with the use of nicotine from any source. Sustained use of nicotine polacrilex preparations or transdermal or orally inhaled nicotine should not be encouraged because chronic consumption of nicotine may result in intoxication and dependence (addiction). In deciding whether to initiate therapy with nicotine polacrilex preparations or transdermal or orally inhaled nicotine, regardless of the presence of disease or pregnancy, the risk of nicotine replacement in a smoking-cessation program should be weighed against the hazard of continued smoking concurrent with nicotine-replacement therapy and the likelihood of achieving smoking cessation without such pharmacologic management.<br><br>*SOURCE: American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)* |

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**DATE OF PREPARATION:** 22 Oct 2018
**CHEMICAL NAME:** Nicotine
**CAS:** 54-11-5

REPORT TITLE: Existence of in vitro and in vivo assays to evaluate the toxicological effects of the ingredient on the heart, blood vessels or respiratory tract.

| KEYWORD | STUDIES |
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| cardiopulmonary | TITLE:<br>Thromboembolic injury and systemic toxicity induced by nicotine in mice.<br><br>ABSTRACT:<br>Nicotine is involved in the pathogenesis of hematological and cardiopulmonary diseases. The understanding of the pathophysiological mechanisms underlying these undesirable effects is however unclear. Cigarette smoking, nicotine gums and patches are common sources for nicotine ingestion. We have investigated the nicotine's effect on cerebral microvessel thrombosis and systemic toxicity. Mice received either nicotine (1 mg/kg, i.p.) or saline (control), once a day for 21 days. Briefly, after bolus intravenous fluorescein injection, a photo insult of cerebral microvessel was done. The platelet aggregation in microvessels was video recorded and analyzed. In conjunction, the plasma levels of superoxide dismutase (SOD), lactate dehydrogenase (LDH), liver enzymes, creatinine and blood urea nitrogen (BUN); and histopathological studies were carried out. Our results revealed a significant prothrombotic effect following nicotine exposure. Significant decrease in SOD indicates the occurrence of oxidative stress involved in the tissue damages and increase in the LDH emphasize the systemic toxicity. Substantial rise in the liver aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were observed. Lungs histology showed intra-vascular hemorrhagic infarction with necrosis, macrophage and neutrophils infiltration. Liver histology showed intravascular thrombosis and portal inflammation. We conclude that the sub-acute nicotine exposure causes an increase in thrombosis in cerebral microvessels and systemic, hepatic and pulmonary toxicity.<br><br>SOURCE:<br>*Gen Physiol Biophys. 2014; 33(3):345-55. [General physiology and biophysics]* |

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**DATE OF PREPARATION:** 22 Oct 2018
**CHEMICAL NAME:** Nicotine
**CAS:** 54-11-5

REPORT TITLE: Existence of studies that indicate the chemistry and/or toxicity of emissions

| KEYWORD | STUDIES |
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| inhalation | Oral inhalation of nicotine from the inhaler commonly produces oropharyngeal irritation. About 32-50% of patients experience oropharyngeal irritation such as coughing and mouth and throat irritation; in controlled studies, such effects occurred in about 12-18% of placebo inhalation recipients. Such irritation appears to be dose related, occurring in 66% of patients receiving higher than currently recommended dosages in clinical studies. At usual dosages, cough occurred in 27-32% of patients during the first week, and mouth and throat irritation occurred in 15% of patients; these effects generally were mild. Such local irritation decreases with continued oral inhalation therapy. Rhinitis, another effect of local irritation, occurred in 23% of patients. Other effects possibly related to local irritant effects of nicotine oral inhalation and occurring in greater than 3% of patients include taste disturbances, jaw and neck pain, tooth disorders, and sinusitis. Local irritant effects generally have been mild and decline in frequency with continued use, but such effects occasionally may be severe enough to result in discontinuance of nicotine oral inhalation therapy.<br><br>*SOURCE: American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)* |
| inhalation | Nicotine oral inhaler has not be studied specifically in patients with asthma or chronic pulmonary disease. Nicotine is an airway irritant and might cause bronchospasm, and local irritation occurs commonly with orally inhaled nicotine. Therefore, nicotine replacement therapy via oral inhalation should be undertaken with caution in patients with bronchospastic disease, and other forms of replacement therapy might be preferable in patients with severe bronchospastic airway disease.<br><br>*SOURCE: American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)*] |
| inhalation | PROBABLE ROUTES OF HUMAN EXPOSURE:<br><br>NIOSH (NOES Survey 1981-1983) has statistically estimated that 4,737 workers (861 of these were female) were potentially exposed to nicotine in the US(1). The NOES Survey does not include farm workers. Occupational exposure to nicotine may occur through inhalation and dermal contact with this compound at workplaces where nicotine is produced or used. Monitoring data indicate that the general population may be exposed to nicotine via inhalation of ambient air. Exposure to nicotine among the general population may be via dermal contact by those using nicotine transdermal patches for the treatment of cigarette smoking withdrawal and by those who smoke cigarettes or are in close proximity of people who are smoking cigarettes(SRC). |

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| | *SOURCE: (1) NIOSH; NOES. National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC). Available at http://www.cdc.gov/noes/ as of Mar 3, 2009.* |
| inhalation | ENVIRONMENTAL FATE & EXPOSURE:<br><br>ENVIRONMENTAL FATE/EXPOSURE SUMMARY:<br><br>Nicotine's production and use as a pharmaceutical may result in its release to the environment through various waste streams; its limited use as an insecticide will result in its direct release to the environment. Nicotine is contained in the leaves of the tobacco plants Nicotiana tabacum and N. rustica. If released to air, a vapor pressure of 0.0038 mm Hg at 25 deg C indicates nicotine will exist solely as a vapor in the atmosphere. Vapor-phase nicotine will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 4 hours. Nicotine does not contain chromophores that absorb at wavelengths > 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight. If released to soil, nicotine is expected to have high mobility based upon an estimated Koc of 100. However, nicotine is a base and protonation under neutral and acidic conditions may result in greater adsorption and less mobility than its estimated Koc or water solubility indicate. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 3.0X10-9 atm-cu m/mole. Nicotine may volatilize from dry soil surfaces based upon its vapor pressure. Nicotine was biodegraded very slowly by Arthrobacter globiformis, isolated from cigar tobacco leaves (var. Nambu) and soil of a tobacco field, to first 6-hydroxynicotine and then 6-hydroxy-N'-methylmyosine. Mixed culture data were not available. If released into water, nicotine is not expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions. Occupational exposure to nicotine may occur through inhalation and dermal contact with this compound at workplaces where nicotine is produced or used. Monitoring data indicate that the general population may be exposed to nicotine via inhalation of ambient air. Exposure to nicotine among the general population may be via dermal contact by those using nicotine transdermal patches for the treatment of smoking withdrawal and by those who smoke cigarettes or are in close proximity of people who are smoking cigarettes. (SRC)<br><br>*SOURCE: HSDB* |
| inhalation | GUIDE 151: SUBSTANCES - TOXIC (Non-combustible)/ Health:<br><br>Highly toxic, may be fatal if inhaled, swallowed or absorbed through skin. Avoid any skin contact. Effects of contact or inhalation may be delayed. Fire may produce irritating, corrosive and/or toxic gases. Runoff from fire control or dilution water may be corrosive and/or toxic and cause pollution.<br><br>*SOURCE: U.S. Department of Transportation. 2012 Emergency Response Guidebook. Washington, D.C. 2012* |
| inhalation | NFPA HAZARD CLASSIFICATION: Health:<br><br>4. 4= Materials that, on very short exposure, could cause death or major residual injury, including those that are too dangerous to be approached without specialized protective equipment. A few whiffs of the vapor or gas can cause death, or contact with the vapor or liquid may be fatal, if it penetrates the fire |

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| | fighter's normal protective gear. The normal full protective clothing and breathing apparatus available to the typical fire fighter will not provide adequate protection against inhalation or skin contact with these materials.<br><br>*SOURCE: Fire Protection Guide to Hazardous Materials. 12 ed. Quincy,MA: National Fire Protection Association, 1997., p. 325-74* |
| inhalation | TITLE:<br>Toxicity of aerosols of nicotine and pyruvic acid (separate and combined) in Sprague-Dawley rats in a 28-day OECD 412 inhalation study and assessment of systems toxicology.<br><br>ABSTRACT:<br>Toxicity of nebulized nicotine (Nic) and nicotine/pyruvic acid mixtures (Nic/Pyr) was characterized in a 28-day Organization for Economic Co-operation and Development 412 inhalation study with additional transcriptomic and lipidomic analyses. Sprague-Dawley rats were nose-only exposed, 6?h/day, 5 days/week to filtered air, saline, nicotine (50?µg/l), sodium pyruvate (NaPyr, 33.9?µg/l) or equimolar Nic/Pyr mixtures (18, 25 and 50?µg nicotine/l). Saline and NaPyr caused no health effects, but rats exposed to nicotine-containing aerosols had decreased body weight gains and concentration-dependent increases in liver weight. Blood neutrophil counts were increased and lymphocyte counts decreased in rats exposed to nicotine; activities of alkaline phosphatase and alanine aminotransferase were increased, and levels of cholesterol and glucose decreased. The only histopathologic finding in non-respiratory tract organs was increased liver vacuolation and glycogen content. Respiratory tract findings upon nicotine exposure (but also some phosphate-buffered saline aerosol effects) were observed only in the larynx and were limited to adaptive changes. Gene expression changes in the lung and liver were very weak. Nic and Nic/Pyr caused few significant changes (including Cyp1a1 gene upregulation). Changes were predominantly related to energy metabolism and fatty acid metabolism but did not indicate an obvious toxicity-related response. Nicotine exposure lowered plasma lipids, including cholesteryl ester (CE) and free cholesterol and, in the liver, phospholipids and sphingolipids. Nic, NaPyr and Nic/Pyr decreased hepatic triacylglycerol and CE. In the lung, Nic and Nic/Pyr increased CE levels. These data suggest that only minor biologic effects related to inhalation of Nic or Nic/Pyr aerosols were observed in this 28-day study.<br><br>SOURCE:<br>*Inhal Toxicol. 2015; 27(9):405-31. [Inhalation toxicology]* |
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| inhalation | The pharmacokinetics of various commercially available dosage forms of nicotine and nicotine polacrilex differ principally in the rate, site, and extent of absorption of the drug, with absorption being most rapid with intranasal administration of the spray (peak concentrations achieved within 4-15 minutes), followed by chewing the gum (peaks within 25-30 minutes) or oral inhalation (peaks within 15-30 minutes), and then being substantially slower with the transdermal systems (peaks within 2-10 hours). Plasma nicotine concentrations fluctuate least with the transdermal systems and are least like those produced by cigarette smoking, whereas those produced by intranasal administration mimic those of cigarette smoking most closely, although the role of their rise is still somewhat slower and peaks achieved generally are lower than with cigarettes.<br><br>*SOURCE: American Society of Health System Pharmacists; AHFS Drug Information 2009. Bethesda, MD. (2009)* |
| vaporized | TITLE:<br>Effects of maternal alcohol consumption on the developing nervous system.<br><br>ABSTRACT:<br>Nicotine is oxidized to cotinine which has a long plasma half-life (19-24 hr) in humans. Cotinine activates phospholipase A2 (PLA2)-like enzymes resulting in formation of prostaglandins (PGE2 and PGF2alpha) which induce abortions. Therefore, we have studied the placental transfer of nicotine and its convertion to cotinine using isolated perfused human cotyledon. The cotyledon was perfused with aerated (21% O2, 5% CO2) Kreb-Ringer bicarbonate buffer (pH 7.4, 37 degrees C) containing 2% albumin on both maternal (230 mL, 15 mL/min, 0.6" Hg) and fetal (93 mL, 1.75 mL/min, 1.75" Hg) sides in a closed recirculating system. Nicotine was added to maternal (2 mg) or fetal (0.81 mg) perfusate and both perfusate samples (1 mL) were analyzed for nicotine and cotinine by HPLC at regular intervals. About 18.6% of nicotine added to the maternal perfusate was transferred to the fetal side in 40 min and the maternal/fetal concentration ration reached 1. About 1% of nicotine was oxidized to cotinine in placenta and cotinine |

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| | concentrations were equal at 100 min. When nicotine was added on the fetal side, part of it was metabolized to cotinine. However, the maximal concentration of cotinine was twice higher in fetal side than in maternal side. These observations suggest that accumulation of cotinine on fetal side may activate PG formation and trigger spontaneous abortions in pregnant smokers. MEDICAL SUBJECT HEADINGS (MESH): Pregnancy Human Female Support, Non-U.S. Gov't Cotinine/*METABOLISM Nicotine/*METABOLISM Nicotine/*TOXICITY Perfusion *Maternal-Fetal Exchange Fetal Blood/*METABOLISM Abortion, Spontaneous/*CHEMICALLY INDUCED<br><br>SOURCE:<br>*Alcohol and Neurobiology: Brain Development and Hormone Regulation 1992;:1-30 MEDICAL SUBJECT HEADINGS (MESH): Pregnancy Animal Human Female Ethanol/*TOXICITY Fetus/*DRUG EFFECTS Brain/*DRUG EFFECTS Astrocytes/DRUG EFFECTS Neurotransmitters/*METABOLISM Neurosecretory Systems/*DRUG EFFECTS* |

The following information was generated from the Toxicology Bibliographic Information (TOXLINE, DART, HSDB, CRIS, GENETOX, IRIS, ITER, LACTMED, CHEMID, CPDB, CTD, HAZMAP, HPD, TOXMAP, TRI2014), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) on 2018-10-22

**DATE OF PREPARATION:** 22 Oct 2018
**CHEMICAL NAME:** Nicotine
**CAS:** 54-11-5

Existence of any other toxicological data.

| KEYWORD | STUDIES |
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| specific target organ toxicity | TITLE:<br>Cytochrome P450 in Nicotine Metabolism<br><br>ABSTRACT:<br>DESCRIPTION (provided by applicant): Tobacco smoking is responsible for more than 400,000 deaths annually in the United States. Nicotine is the major addictive agent in tobacco, the key ingredient that maintains smoking behavior. Individual differences in nicotine metabolism affect smoking behavior and potentially nicotine addiction. Nicotine is primarily metabolized by 5'-oxidation. P450 2A6 is the major hepatic catalyst of this reaction, and we recently reported that P450 2A13, a lung P450, is also a good catalyst. An unexpected and exciting outcome of these studies was that nicotine was a mechanism-based (suicide) inhibitor of P450 2A6 and P450 2A13. Determining the mechanism of this inhibition is the primary goal of this grant. However, to begin to investigate the impact of nicotine-mediated inactivation on whole tissue metabolism, we will study P450 2A3 inactivation in the perfused rat lung. P450 2A3 (89% identical to P450 2A13) is an excellent catalyst of nicotine metabolism. Our hypothesis is that inactivation of P450 2A6, P450 2A13 and P450 2A3 occurs through a common mechanism and that any differences in inactivation are due to differences in the specificity and catalytic efficiency of these enzymes. Nicotine 5'-oxidation, as well as minor pathways of 2'- and methyl oxidation, generates reactive iminium ions, all possible inactivating molecules. However, preliminary data support a metabolite of the ?5'(1') iminium ion, as the inactivating species. This grant will investigate what pathway of nicotine metabolism is responsible for enzyme inactivation and how P450 2A3 inactivation affects the metabolic capacity of the rat lung. The Specific aims are: 1. To characterize the secondary products of nicotine metabolism and determine their role in inactivation. 2. To determine if modification of the heme and/or apoprotein occurs during nicotine-mediated inactivation of P450 2A enzymes, both Mass Spectrometry and NMR analyses will be carried out. 3. To establish the rat lung as a model system in which to investigate potential in vivo effects of nicotine-mediated P450 2A inactivation. The characterization of nicotine-mediated inactivation of P450 2A6 and 2A13 is critical to an accurate and complete understanding of nicotine metabolism in smokers. In addition, identifying the mechanism by which this occurs will aid in the design of nicotine analogs as enzyme inhibitors and potential medications for treatment of nicotine addiction. Also of key importance, is that the inactivation of P450 2A enzymes will impact the metabolism of the tobacco specific carcinogens, NNK and NNN.<br><br>SOURCE:<br>*RePORTER Database National Institutes of Health* |
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| cytotoxicity | TITLE:<br>Nicotine protects cultured cortical neurons against glutamate-induced cytotoxicity via alpha7-neuronal receptors and neuronal CNS receptors.<br><br>ABSTRACT:<br>We examined the effects of nicotine on glutamate-induced cytotoxicity using primary cultures of rat cortical neurons. The cell viability decreased significantly when cultures were exposed to glutamate for 10 min and then incubated with glutamate-free medium for 1 h. The exposure of cultures to nicotine (10 microM) for 8-24 h prior to glutamate application ameliorated the glutamate-induced cytotoxicity, with no significant effect of nicotine alone on the cell viability. Neuroprotection by nicotine was dependent on the incubation period. alpha-bungarotoxin (alpha-BTX) and methyllycaconitine (MLA), both of which are alpha7-neuronal receptor antagonists, and dihydro-beta-erythroidine (DHbetaE), a neuronal central nervous system (CNS) receptor antagonist, each significantly antagonized the protection by nicotine against glutamate-induced cytotoxicity. Ionomycin, a calcium ionophore, and S-nitrosocysteine (SNOC), a nitric oxide (NO) donor, also induced cytotoxicity in a manner similar to glutamate. Nicotine protected cultures against ionomycin-induced cytotoxicity, but not against SNOC-induced cytotoxicity. These results suggest that nicotine protects cultured cortical neurons against glutamate-induced cytotoxicity via alpha7-neuronal receptors and neuronal CNS receptors by reducing NO-formation triggered by Ca2+ influx.<br><br>SOURCE:<br>*Brain Res. 1997, Aug 08; 765(1):135-40. [Brain research]* |
| inhalation | TITLE:<br>Toxicity of aerosols of nicotine and pyruvic acid (separate and combined) in Sprague-Dawley rats in a 28-day OECD 412 inhalation study and assessment of systems toxicology.<br><br>ABSTRACT:<br>Toxicity of nebulized nicotine (Nic) and nicotine/pyruvic acid mixtures (Nic/Pyr) was characterized in a 28-day Organization for Economic Co-operation and Development 412 inhalation study with additional transcriptomic and lipidomic analyses. Sprague-Dawley rats were nose-only exposed, 6?h/day, 5 days/week to filtered air, saline, nicotine (50?µg/l), sodium pyruvate (NaPyr, 33.9?µg/l) or equimolar Nic/Pyr mixtures (18, 25 and 50?µg nicotine/l). Saline and NaPyr caused no health effects, but rats exposed to nicotine-containing aerosols had decreased body weight gains and concentration-dependent increases in liver weight. Blood neutrophil counts were increased and lymphocyte counts decreased in rats exposed to nicotine; activities of alkaline phosphatase and alanine aminotransferase were increased, and levels of cholesterol and glucose decreased. The only histopathologic finding in non-respiratory tract organs was increased liver vacuolation and glycogen content. Respiratory tract findings upon nicotine exposure (but also some phosphate-buffered saline aerosol effects) were observed only in the larynx and were limited to adaptive changes. Gene expression changes in the lung and liver were very weak. Nic and Nic/Pyr caused few significant changes (including Cyp1a1 gene upregulation). Changes were predominantly related to energy metabolism and fatty acid metabolism but did not indicate an obvious toxicity-related response. Nicotine exposure lowered plasma lipids, including cholesteryl ester (CE) and free cholesterol and, in the liver, phospholipids and sphingolipids. Nic, NaPyr and Nic/Pyr decreased hepatic triacylglycerol and CE. In the lung, Nic and Nic/Pyr increased CE levels. These data suggest that only minor biologic effects related to inhalation of Nic or Nic/Pyr aerosols were observed in this 28-day study.<br><br>SOURCE:<br>*Inhal Toxicol. 2015; 27(9):405-31. [Inhalation toxicology]* |

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| acute oral toxicity | TITLE:<br>Acute intoxication due to chemical substances and their treatments. Intoxication due to agricultural chemicals (pesticides), especially by organofluorines, arsenicals and nicotine.<br><br>ABSTRACT:<br>PESTAB. The biochemistry and toxicological action of organofluorine, arsenical and nicotinic pesticides are reviewed. The mouse oral LD50 values of representative compounds from each group are given in tabular form. Organofluorines had LD50 values ranging from 1-7 (for sodium fluoroacetate) to 410 mg/kg (for N- (p-bromobenzyl) fluoroacetamide). Arsenical LD50's ranged from 50 (for calcium arsenate) to 2000-5000 mg/kg (for iron methane arsenate), and nicotinic LD50 values ranged from 24 (for nicotine) to 563 mg/kg (for anabasine). Acute toxicity symptoms of each type of pesticide are given and the actions of the pesticides on acetylcholine receptors and diagnosis and treatment of poisoning by these compounds are also discussed.<br><br>SOURCE:<br>*Gekkan Yakuji (Pharmaceut. Mo.) 21(10): 2023-2028 1979 (5 References)* |
| eye irritation | TITLE:<br>Nicotine<br><br>ABSTRACT:<br>International chemical safety card. Short-term exposure effects: skin absorption; delayed effects; irritation of the eyes and skin; neurotoxic effects (central nervous system); convulsions; respiratory insufficiency. Occupational exposure limits: TLV: 0.5mg/m\|3\| (TWA) (skin) (ACGIH 1991-1992).<br><br>SOURCE:<br>*Official Publications of the European Communities, 2985 Luxembourg, Grand Duchy of Luxembourg; International Programme on Chemical Safety (IPCS), World Health Organization, 1211 Gen?eve 27, Switzerland, 1993. 2p.* |
| specific target organ toxicity | TITLE:<br>Nicotine Increases CYP2B In The Brain But Not In The Liver: Contrasting The Regulation In Rodents, Non-Human Primates And People.<br><br>ABSTRACT:<br>Approximately 25% of adult Americans smoke daily. Nicotine is consumed not only by smokers, but also by passive smokers and ex-smokers on nicotine replacement therapies (NRTs), and NRTs are in clinical trials for the treatment of a number of neurological diseases. The metabolism of drugs and toxins can be substantially altered by enzyme induction by constituents of tobacco smoke such as nicotine. We have found that in rat, low, behaviorally relevant doses of nicotine given for 7 days (s.c.) increase CYP2B in the brains but not in the livers. The induction by nicotine in the brain is specific for both cell-type and brain region. The elevation in brain CYP2B protein, determined by western blotting and immunocytochemistry, is dose-dependently related to increased CYP2B1 mRNA. These data suggest that the regulation of CNS CYP2B by nicotine involves transcriptional mechanisms. In human brain, we have found brain region- and cell type-specific distributions of CYP2B6. We also have found elevated levels of CYP2B6 in the brains from smokers, compared to non-smokers. The regional and cellular localization of brain CYP2B6 in smokers differs from the regional and cellular localization of nicotine-induced CYP2B in the rat brain. To investigate this further, we treated non-human primates (African Green Monkeys) with nicotine and are currently investigating the presence and induction by nicotine of CYP2B in liver and brain. As predicted from rat and human data, there is no elevation of |

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| | CYP2B in monkey liver. Data derived from the monkey brain should help us to differentiate species effects (rodent versus primate) from inducer effects (nicotine versus cigarette smoking), and allow us to validate the African Green Monkey as a model for human smokers. Funded by CIHR MT 14173 and by a Canadian Research Chair in Pharmacogenetics to RFT. ENZYME CLASSIFICATION: Cytochrome P-450 CYP2B1; EC 1.14.14.1 S-mephenytoin N-demethylase; EC 1.14.14.1 MEDICAL SUBJECT HEADINGS (MESH): Rats Animals Humans Cercopithecus aethiops *Nicotine/ADVERSE EFFECTS/TOXICITY Brain/*DRUG EFFECTS/ENZYMOLOGY Liver/*DRUG EFFECTS/ENZYMOLOGY Cytochrome P-450 CYP2B1/*BIOSYNTHESIS Oxidoreductases, N-Demethylating/*BIOSYNTHESIS Aryl Hydrocarbon Hydroxylases/*BIOSYNTHESIS Enzyme Induction/DRUG EFFECTS Organ Specificity Species Specificity Research Support, Non-U.S. Gov't<br><br>SOURCE:<br>*Toxicologist 2004 Mar;78(1-S):194* |